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SEE PAGE 422

DISPLAY SHELVES

The Western Journal of Medicine

VOLUME 147 • NUMBER 4 OCTOBER 1987

CLINICAL INVESTIGATION

423 Mapping Approaches to Gene Identification in Humans
R L WHITE, J-M LALOUEL, M LATHROP, M F LEPPERT, Y NAKAMURA and P O'CONNELL

CLINICAL MEDICINE

428 Patterns of Cervical Spine Injury and Their Associated Lesions
A N GUTHKELCH and A S FLEISCHER

432 Oral Cholecystography and Sonography of Gallbladder in Cholecystectomy Patients
A ROBLES, D DEVOR, H WANG and C WARREN

MEDICAL PROGRESS

435 Nutrition of the Fetus and Newborn
J M KENNAUGH and W W HAY, Jr

MEDICAL STAFF CONFERENCE

449 Diabetes, Dietary Protein and Glomerular Hyperfiltration
Discussants: B R DON and M SCHAMBELAN

EPITOMES

456 Important Advances in Dermatology

EDITORIALS

462 • Light at the End of the Tunnel?
• The Geneticist's Grail
• Nutrition During the Continuum of Development

CASE REPORTS

466 Influenza B Encephalitis
W H BAYER

467 Maxillary Sinusitis—The Focus of Toxic Shock Syndrome in a Male Patient
S D WOOD, K RIES, G L WHITE, Jr, R T MURDOCK and D M PEDERSEN

469 *Plasmodium vivax* Malaria From Mexico—A Problem in the United States
J BRILLMAN

CORRESPONDENCE

474 • Pain Control in Cancer Patients
• Tracheostomy Tube Failure
• Soviet Health Care
• Fear of the Unknown

TOPICS IN PRIMARY CARE MEDICINE

477 Exercise in the Elderly
M E WHEAT

MEDICAL SCHOOLS OF THE WEST

481 Oregon Health Sciences University School of Medicine Celebrates Centennial
F W LEONHARDT and D E WARD

COMMENTARY

486 Genetic Markers in Huntington's Disease
E M FROHMAN and J B MARTIN

HEALTH CARE DELIVERY

487 Does a Helicopter Service Stimulate Financially Motivated Transfers?
K J RHEE, R J O'MALLEY, J E TURNER, N H WILLITS and R E WARD

OTHER FEATURES

416 Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming

420 In Memoriam

495 Subscription Information

500 Classified Advertising

510 Western State Medical Associations' Meetings

Detailed Table of Contents: 395, 399, 400

Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.

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The portrait of anxiety

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Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

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is often complicated

With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

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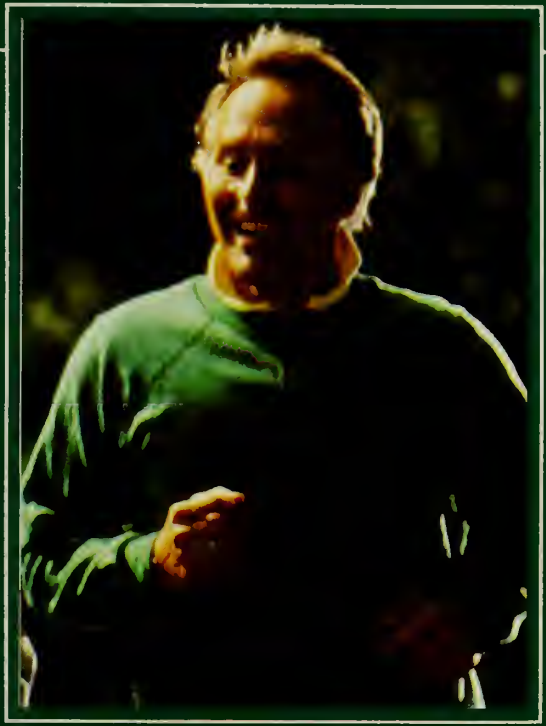

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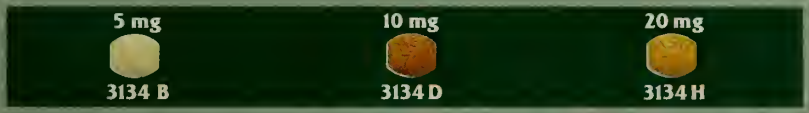

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Usually No Interference with Physical or Mental Activity

Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC—a fact that may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.

Also, certain central effects, such as impairment of memory, nightmares, or depression, have not been characteristic of VASOTEC.

ACE* Inhibition That Favorably Affects Certain Hemodynamic Parameters in Many Patients

VASOTEC has a highly specific mode of action which acts on the renin-angiotensin-aldosterone system—it blocks ACE from converting angiotensin I to angiotensin II, one of the most potent vasoconstrictors known. For many hypertensive patients, VASOTEC favorably affects certain hemodynamic parameters: peripheral arterial resistance is reduced with an increase in cardiac output and no significant change in heart rate; sodium and water retention are also reduced.

VASOTEC is contraindicated in patients who are hypersensitive to this product.

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme (ACE) inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC in clinical trials). In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. In using VASOTEC, consideration should be given to the fact that another ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and the available data are insufficient to show that VASOTEC does not have a similar risk (see WARNINGS).

Discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

*angiotensin-converting enzyme

FOR MANY HYPERTENSIVE PATIENTS

ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

IT MAY HELP CHANGE THE WAY YOU MANAGE YOUR HYPERTENSIVE PATIENTS

TIENTS FEEL

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSO) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose. (See WARNINGS and DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC® (Enalapril Maleate, MSO) has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials or since the drug was marketed include:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Renal: Renal dysfunction, renal failure, oliguria. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Other: Dyspnea, muscle cramps, hyperhidrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Dosage and Administration: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg (break the 5-mg tablet) should be used under medical supervision for at least one hour to determine whether excess hypotension will occur. (See WARNINGS and PRECAUTIONS, *Drug Interactions.)*

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily. For dialysis patients, the initial dose and the dose on dialysis days is 2.5 mg/day. Dosage on nondialysis days should be adjusted depending on blood pressure response.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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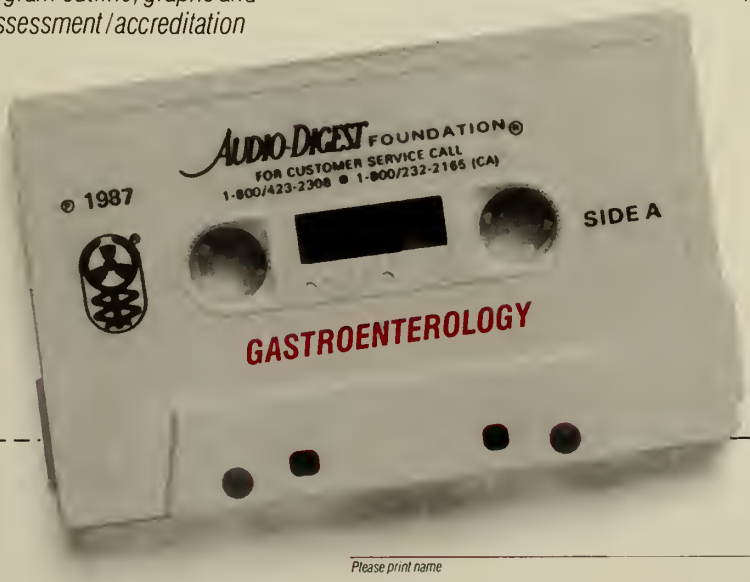

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CONTENTS

CLINICAL INVESTIGATION

423 **Mapping Approaches to Gene Identification in Humans**
RAYMOND L. WHITE, PhD; JEAN-MARC LALOUEL, MD, ScD; G. MARK LATHROP, PhD; MARK F. LEPPERT, PhD; YUSUKE NAKAMURA, MD, and PETER O'CONNELL, PhD
From the Department of Human Genetics, Howard Hughes Medical Institute, University of Utah School of Medicine, Salt Lake City.

CLINICAL MEDICINE

428 **Patterns of Cervical Spine Injury and Their Associated Lesions**
A. NORMAN GUTHKELCH, FRCS, and ALAN S. FLEISCHER, MD
From the Section of Neurosurgery, Department of Surgery, University of Arizona Health Sciences Center, Tucson.

432 **Oral Cholecystography and Sonography of Gallbladder in Cholecystectomy Patients**
ANTONIO ROBLES, MD; DANIEL DEVOR, MD; HANSEN WANG, MD, and CHARLES WARREN, MD
From the Department of Surgery, Kaiser Permanente Medical Center, Fontana, California.

MEDICAL PROGRESS

435 **Nutrition of the Fetus and Newborn**
JAN M. KENNAUGH, MD, and WILLIAM W. HAY, Jr, MD
From the Department of Pediatrics, Division of Perinatal Medicine, University of Colorado Health Sciences Center, and The Children's Hospital, Denver.

MEDICAL STAFF CONFERENCE

449 **Diabetes, Dietary Protein and Glomerular Hyperfiltration**
Discussants: BURL R. DON, MD, and MORRIS SCHAMBELAN, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Dermatology
Items of progress in dermatology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

456 **Removing Tattoos**
KENNETH G. GROSS, MD

457 **Lyme Disease**
DENNY L. TUFFANELLI, MD

457 **Ketoconazole Use in Tinea Versicolor**
PAUL H. JACOBS, MD

457 **Recent Advances in Clinical Use of Retinoids**
NICHOLAS J. LOWE, MD

458 **Liposuction in Dermatology**
SAMUEL J. STEGMAN, MD

(Continued on Page 399)

***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

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Means a feeling of well-being.

Well-being—a feeling difficult to describe when it's present; easy to spot when it's gone. CAPOTEN improved hypertensive patients' sense of general well-being.[1] CAPOTEN had a positive effect on patients' vitality and general health. In fact, all measures of well-being studied showed a trend toward improvement.[2]

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CAPOTEN—things are looking up for patients who need to keep their blood pressure down.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

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(Continued from Page 395)

458 **Using Lasers in Skin Surgery**
NORMAN LEVINE, MD

459 **Dysplastic Nevi—Markers and Precursors of Malignant Melanoma**
WILLIAM A. CRUTCHER, MD

459 **Contraindications for Using Topical Steroids**
ROGER C. CORNELL, MD

460 **Bowenoid Papulosis**
DAVID A. SOUTH, MD

460 **Cutaneous Manifestations of the Acquired Immunodeficiency Syndrome (AIDS) and AIDS-Related Conditions**
S. IRA GREENE, MD

461 **Short-Contact Anthralin Therapy for Psoriasis**
HEIDI E. FLEISCHMANN, MD

EDITORIALS

462 **Light at the End of the Tunnel?**

462 **The Geneticist's Grail**
EDWARD M. RUBIN, MD, PhD, and YUET W. KAN, MD, DSc
From the Howard Hughes Medical Institute and the Departments of Pediatrics and Medicine, University of California, San Francisco.

463 **Nutrition During the Continuum of Development**
FRANK H. MORRISS, Jr, MD
From the Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City.

CASE REPORTS

466 **Influenza B Encephalitis**
WILLIAM H. BAYER, MD
From the Family Practice Residency of Idaho, Boise, and the Department of Family Medicine, University of Washington School of Medicine, Seattle.

467 **Maxillary Sinusitis—The Focus of Toxic Shock Syndrome in a Male Patient**
STEPHEN D. WOOD, MD; KRISTEN RIES, MD; GEORGE L. WHITE, Jr, PhD; RICHARD T. MURDOCK, MHA, and DONALD M. PEDERSEN, MS
From the Utah MEDEX Project, Department of Family and Preventive Medicine, University of Utah School of Medicine, and the Utah Medical Association, Salt Lake City.

469 ***Plasmodium vivax* Malaria From Mexico—A Problem in the United States**
JUDITH BRILLMAN, MD
From the Division of Emergency Medicine, Stanford University Medical Center, Stanford, California.

CORRESPONDENCE

474 **Pain Control in Cancer Patients**
AMBER ARLINGTON, MPH, MD
MALCOLM L. BRIGDEN, MD, and JEFFREY B. BARNETT, BScPharm, Reply

475 **Tracheostomy Tube Failure**
DAVID M. ALESSI, MD, and GERALD BERKE, MD
E. FRITZ SCHMERL, MD

(Continued on Page 400)

(Continued from Page 399)

475 **Soviet Health Care**
THEODORE B. MASSELL, MD

475 **Fear of the Unknown**
IRA E. BAILIE, MD

TOPICS IN PRIMARY CARE MEDICINE

477 **Exercise in the Elderly**
MARY E. WHEAT, MD
From the Department of Medicine, Montefiore Medical Center, Bronx, New York.

MEDICAL SCHOOLS OF THE WEST

481 **Oregon Health Sciences University School of Medicine Celebrates Centennial**
FRED W. LEONHARDT and DARRELL E. WARD, MS
From the Office of University Communications, Oregon Health Sciences University, Portland.

COMMENTARY

486 **Genetic Markers in Huntington's Disease**
ELLIOT M. FROHMAN and JOSEPH B. MARTIN, MD, PhD
From the 4th Year MD/PhD Program, Departments of Neurology, Anatomy and Neurobiology, University of California, Irvine, California College of Medicine, and the Neurology Service, Massachusetts General Hospital, Harvard Medical School, Boston.

HEALTH CARE DELIVERY

487 **Does a Helicopter Service Stimulate Financially Motivated Transfers?**
KENNETH J. RHEE, MD; ROBERT J. O'MALLEY, RN; JAMES E. TURNER, MD; NEIL H. WILLITS, PhD, and RICHARD E. WARD, MD
From the Division of Critical Care, Emergency Medicine, Department of Internal Medicine, the Division of Statistics, and the Department of Surgery, University of California, Davis, Medical Center, Sacramento.

OTHER FEATURES

416 **Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming**

420 **In Memoriam**

495 **Subscription Information**

500 **Classified Advertising**

510 **Western State Medical Associations' Meetings**

★ Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Only one tablet at bedtime

Controls nocturnal acid to relieve pain and heal duodenal ulcers

Heals active duodenal ulcers after 4 weeks in most patients*[1]

ZANTAC 300 mg h.s.	270/320	84%
ZANTAC 150 mg b.i.d.	292/345	85%

In well-controlled, double-blind, multicenter trials, ZANTAC 300 mg h.s. healed active duodenal ulcers in 84% of patients after 4 weeks. After 8 weeks, healing rates may be higher with ZANTAC 150 mg b.i.d. (92%) than with ZANTAC 300 mg h.s. (87%).

Relieves pain and other symptoms as effectively as ZANTAC 150 mg b.i.d.[1]

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Once-daily dosing may enhance compliance in patients for whom dosing convenience is important

Side-effects profile comparable to ZANTAC 150 mg b.i.d.[1-3]

Headache—sometimes severe—has been reported. Rare effects on the CNS, cardiovascular, GI, hepatic, and integumental systems have been observed, as well as rare cases of hypersensitivity reactions. See ADVERSE REACTIONS section of Brief Summary of Product Information before prescribing.

No significant interference with the hepatic cytochrome P-450 enzyme system at recommended doses

ZANTAC 300 mg h.s. had no significant drug interactions with theophylline or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications which decrease gastric acidity are administered.

It is not known exactly how much acid inhibition is needed to heal ulcers

Glaxo / ROCHE

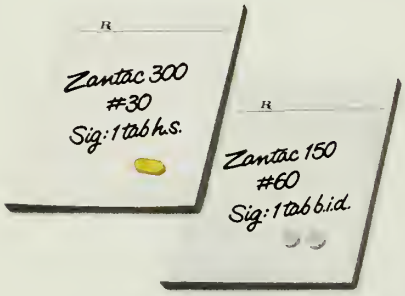
See next page for references and Brief Summary of Product Information

IN ACTIVE DUODENAL ULCERS

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets

Two effective regimens to treat active duodenal ulcers:



References: 1. Data available on request, Glaxo Inc. **2.** Ireland A, Colin-Jones DG, Gear P, et al: Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984;2:274-275. **3.** Colin-Jones DG, Ireland A, Gear P, et al: Reducing overnight secretion of acid to heal duodenal ulcers. *Am J Med* 1984; 77 (suppl 5B):116-122.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, p dominantly in severely ill elderly patients. Rare cases of reversi blurred vision suggestive of a change in accommodation ha been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and p mature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, a abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to least twice the pretreatment levels in 6 of 12 subjects receiv 100 mg qid IV for seven days, and in 4 of 24 subjects receiv 50 mg qid IV for five days. With oral administration there ha been occasional reports of reversible hepatitis, hepatocellular hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, gran locytopenia, thrombocytopenia) have occurred in a few patien Rare cases of agranulocytosis or of pancytopenia, sometimes w marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown stimulation of any pituitary hormone by ZANTAC® (ranitid hydrochloride) and no antiandrogenic activity, and cimetidin induced gynecomastia and impotence in hypersecretory patien have resolved when ZANTAC has been substituted. Howev occasional cases of gynecomastia, impotence, and loss of lib have been reported in male patients receiving ZANTAC, but t incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of m erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospas fever, rash, eosinophilia) and small increases in serum creatinin

OVERDOSAGE: Information concerning possible overdosage and treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The curre recommended adult oral dosage is 150 mg twice daily. An alte nate dosage of 300 mg once daily at bedtime can be used f patients in whom dosing convenience is important. The adva tages of one treatment regimen compared to the other in a particu lar patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosag is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellis syndrome): The current recommended adult oral dosage is 150 m twice a day. In some patients it may be necessary to administe ZANTAC® 150-mg doses more frequently. Doses should b adjusted to individual patient needs, and should continue as lon as clinically indicated. Doses up to 6 g/day have been employed i patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosag is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 m twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On th basis of experience with a group of subjects with severely impaire renal function treated with ZANTAC, the recommended dosag in patients with a creatinine clearance less than 50 ml/min i 150 mg every 24 hours. Should the patient's condition require, th frequency of dosing may be increased to every 12 hours or eve further with caution. Hemodialysis reduces the level of circulatin ranitidine. Ideally, the dosage schedule should be adjusted so th the timing of a scheduled dose coincides with the end of hemodia ysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochlorid equivalent to 300 mg of ranitidine) are yellow, capsule-shape tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40 and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent t 150 mg of ranitidine) are white tablets embossed with "ZANTA 150" on one side and "Glaxo" on the other. They are available i bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs o 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protec from light. Replace cap securely after each opening.

August 198

Glaxo
Glaxo Inc.
Research Triangle Park, NC 27709

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24-hour security for the hypertensive heart

First-step cardiovascular protection

Reduces workload of the heart by reducing myocardial O_2 demand

Preserves K^+ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please consult Brief Summary of Prescribing Information on the following page.

Once-a-day in hypertension...

Lopressor®
metoprolol tartrate

Changing the Course of Cardiovascular Care

Geigy

First-step protection for the hypertensive heart

Lopressor®
metoprolol tartrate USP

Tablets
Ampuls
Prefilled Syringes

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**)
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block, significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg, or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously Both digitalis and Lopressor slow AV conduction

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken Patients should be warned against interruption or discontinuation of therapy without the physician's advice Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who *do* not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e g , tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients, this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block Acute myocardial infarction also produces heart block

If heart block occurs, Lopressor should be discontinued and atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined, (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e g , reserpine) may have an additive effect when given with beta-blocking agents Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia Neither finding represents symptoms of a known disease entity in man In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55 5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients Depression has been reported in about 5 of 100 patients Mental confusion and short-term memory loss have been reported Headache, nightmares, and insomnia have also been reported

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations, congestive heart failure, peripheral edema; and hypotension have been reported in about 1 of 100 patients (See **CONTRAINDICATIONS, WARNINGS**, and **PRECAUTIONS**)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**)

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15 9%	6.7%
Second- or third-degree heart block	4 7%	4 7%
First-degree heart block (P-R ≥ 0.26 sec)	5 3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death

Oral LD_{50}'s (mg/kg): mice, 1158-2460, rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**)

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed

Bradycardia: Atropine should be administered If there is no response to vagal blockade, isoproterenol should be administered cautiously

Hypotension: A vasopressor should be administered, e.g , levarterenol or dopamine

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered

Cardiac Failure: A digitalis glycoside and diuretic should be administered In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered

Geigy

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

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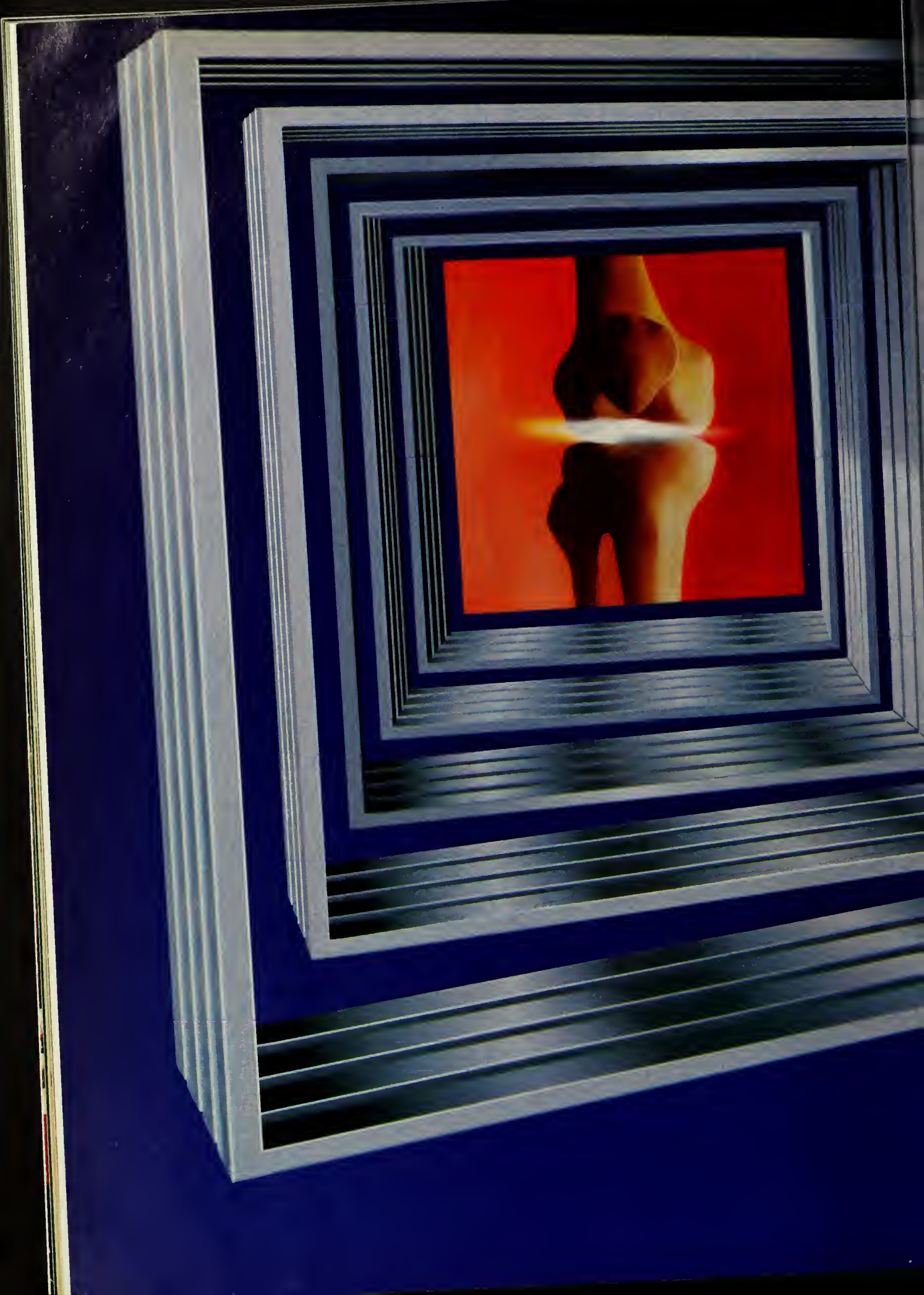

Osteoarthritis and the anti-inflammatory threshold of Motrin

Inflammation is usually a factor in the pain of osteoarthritis. There's ample evidence of this,[1-5] and it may explain why some patients require higher, anti-inflammatory doses of MOTRIN Tablets (ibuprofen).

Studies and experience have shown that at dosages up to 1200 mg/day, ibuprofen is primarily analgesic. Anti-inflammatory activity is added to effective analgesia in patients taking higher dosages of MOTRIN.[6-8]

MOTRIN 800 mg tablets: An easier way to reach the anti-inflammatory range

Extra-strength MOTRIN 800 mg tablets are a more convenient way to provide the higher doses required to maintain anti-inflammatory activity.

Just one 800 mg tablet t.i.d. provides 2400 mg/day for osteoarthritis patients who require higher doses of MOTRIN. If necessary, patients can take one tablet q.i.d. Doses above 3200 mg/day are not recommended. The lowest effective dosage should be used. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin.

Please turn the page for references and a brief summary of prescribing information.

A stronger reason to prescribe MOTRIN in osteoarthritis

Motrin® 800 mg TABLETS
ibuprofen

© 1986 The Upjohn Company

For the inflammation and the pain of osteoarthritis

Motrin® 800 mg TABLETS
ibuprofen

A stronger reason to prescribe MOTRIN.

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MOTRIN® Tablets
(ibuprofen)

CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MOTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship

GASTROINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1% Probable Causal Relationship*

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1% – Causal Relationship Unknown*

GASTROINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

HOW SUPPLIED:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
Bottles of 500	Bottles of 500	Bottles of 100
Unit-dose package of 100	Unit-dose package of 100	Bottles of 500
Unit of Use bottles of 100	Unit of Use bottles of 100	

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

For additional product information, see your Upjohn representative or consult the package insert.

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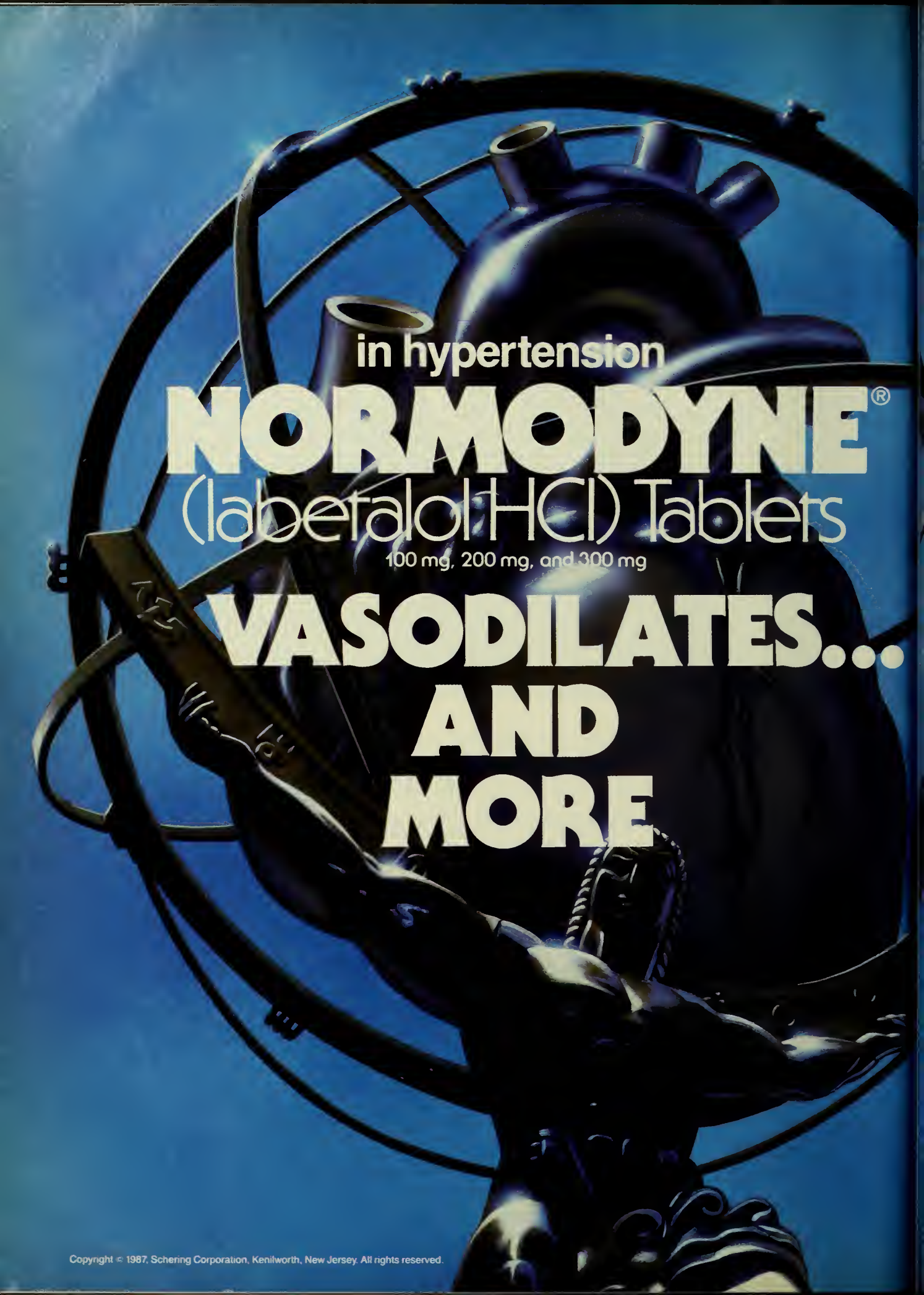

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- beta blockade minimizes risk of reflex tachycardia
- produces no adverse effect on HDL, cholesterol, or triglycerides
- does not impair renal function

...and supports your patients' life-styles

- maintains exercise capacity yet blunts surges in heart rate
- demonstrates a low incidence of impotence, fatigue, and cold extremities*

*Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, the most common side effects noted in treating mild to moderate hypertension with NORMODYNE (labetalol HCl) Tablets include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%), nasal stuffiness (3%), impotence (1%), and drowsiness (<1%) have occurred to a lesser degree. Overall, reports of symptomatic postural hypotension have been uncommon and have included rare instances of syncope. For complete side effects profile, see Prescribing Information.

NORMODYNE®
(labetalol HCl) Tablets

For Brief Summary, please see following page.

13071942-JBS

PRODUCT INFORMATION

NORMODYNE®
brand of labetalol hydrochloride

Tablets
BRIEF SUMMARY

INDICATIONS AND USAGE
NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS
NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS
Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS
General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients
As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests
As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions
In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions
The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C
Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery
Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers
Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	800	900	1200	1600	2400
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticaria; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS**.

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE
Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION
DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED
NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

For complete prescribing information, please consult package insert.

Schering Corporation
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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 15—**Current Perspectives: Wellness.** Little America, Flagstaff. Thurs. Contact: ArMA.

October 23-24—**Therapeutic Dilemmas in the Elderly: What Are the Options?** Boswell Memorial Hospital Support Services Building, Sun City. Fri-Sat. Contact: Western Division, American Geriatrics Society, (602) 977-1877.

November 5-7—**Gynecologic Surgery: Principles, Techniques and Management of Complications.** Hyatt Regency, Scottsdale. Thurs-Sat. Contact: Robin Murray, ACOG, (202) 638-5577, ext 343.

November 13-15—**Bone and Joint Disorders.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Maricopa Medical Center, (602) 267-5361.

November 16-17—**Update on Management of Spina Bifida.** La Posada Resort, Scottsdale. Mon-Tues. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800)-BARROW-1.

January 22-24—**14th Annual Sports Medicine Symposium.** Holiday Inn Metrocenter, Phoenix. Fri-Sun. Contact: ArMA.

February 1-3—**State of the Art 2D/Doppler and Color Flow Imaging.** Sheraton El Conquistador Resort, Tucson. Mon-Wed. Contact: American College of Cardiology, (800) 253-4636, ext 226

February 4-6—**14th Annual Frontiers in Ophthalmology.** Scottsdale Hilton, Scottsdale. Thurs-Sat. Contact: Campbell Meeting Management for St Luke's Medical Center, (602) 838-6728.

March 2-4—**11th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Secretary, Phoenix OB/GYN Society, (602) 241-1917.

March 6-9—**2nd Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sun-Wed. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1

March 7-9—**Practical Cardiology for the Family Physician.** La Posada Resort Hotel, Scottsdale. Mon-Wed. Contact: American College of Cardiology, (800) 253-4636, ext 226.

March 10-12—**15th Annual Symposium: Selected Topics in Ischemic and Hemorrhagic Cerebrovascular Disease.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

PATHOLOGY

November 14-15—**Modern Applications of Immunohistochemistry in Human Tumor Diagnosis.** Arizona Society of Pathologists and U of A at Scottsdale Hilton, Scottsdale. Sat-Sun. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

October 18-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Kauai, Hawaii. Sun-Fri. 20 hrs. $375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 490)

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INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea and vomiting. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued. In some patients, dermatitis may occur.

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Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.
The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.
The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.
Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

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5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26) *100 Systems (NDC 0083-2105-30)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26) *100 Systems (NDC 0083-2110-30)
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*Hospital Pack 100's

C85-35 (Rev. 11/85)

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Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

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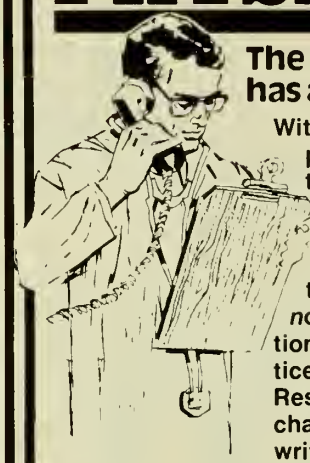
C I B A

PHYSICIANS



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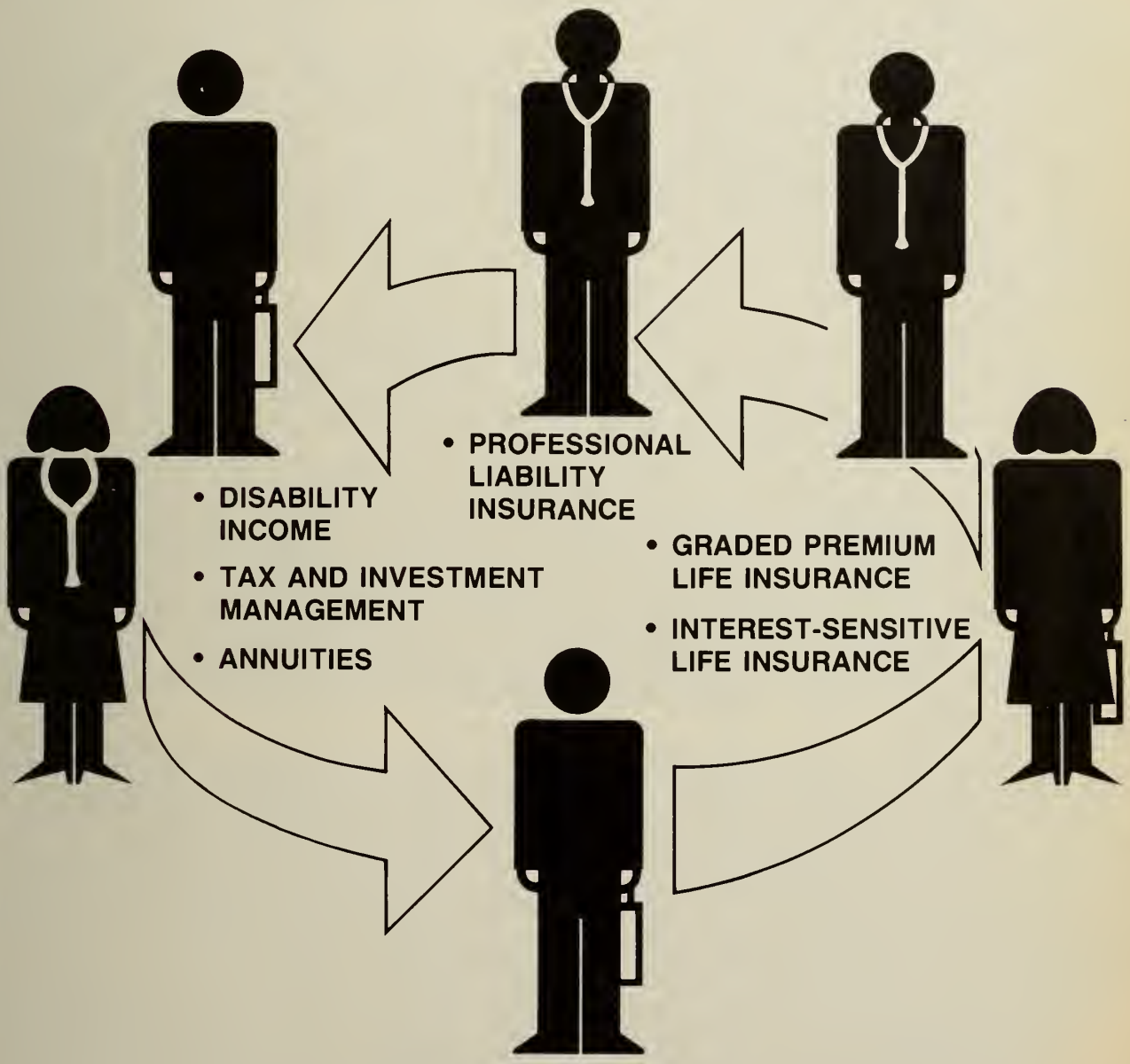

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In Memoriam

California Medical Association

BAZILAUSKAS, V. FAUSTIN. Died Jun 20, 1987, aged 72. Graduate of State University of New York, Downstate, Brooklyn, 1942. Licensed in California in 1952. Dr Bazilauskas was a member of the Los Angeles County Medical Association.

❧

BEAN, JOSEPH PATRICK, Los Angeles. Died Jun 24, 1987, aged 72. Graduate of University of California, Irvine. Dr Bean was a member of the Los Angeles County Medical Association.

❧

CANELO, C. KELLY, San Jose. Died Jun 13, 1987, aged 91. Graduate of St Louis University School of Medicine, 1923. Licensed in California in 1923. Dr Canelo was a member of the Santa Clara County Medical Society.

❧

CRANE, JAY J. Died Jun 25, 1987, aged 94. Graduate of Rush Medical College, Chicago, 1920. Licensed in California in 1921. Dr Crane was a member of the Los Angeles County Medical Association.

❧

CUNNINGHAM, BERNARD P., San Diego. Died Jun 1987, aged 75. Graduate of New York University School of Medicine, 1936. Licensed in California in 1947. Dr Cunningham was a member of the San Diego County Medical Society.

❧

DUNBAR, WILLIAM H., IV, Santa Barbara. Died May 20, 1987, aged 45. Graduate of Temple University, Philadelphia, 1968. Licensed in California in 1971. Dr Dunbar was a member of the Santa Barbara County Medical Society.

❧

DUNIEVITZ, MAX, Auburn. Died Jun 19, 1987, aged 91. Graduate of University of California, San Francisco. Dr Dunievitz was a member of the Placer-Nevada County Medical Society.

❧

HAINS, WILLIAM L., Santa Ana. Died May 29, 1987, aged 58. Graduate of California College of Medicine, 1962. Dr Hains was a member of the Orange County Medical Association.

❧

HORTON, ROGER E. Died Apr 23, 1987, aged 53. Graduate of University of Southern California, 1960. Licensed in California in 1961. Dr Horton was a member of the Los Angeles County Medical Association.

❧

KENNEY, JOHN MEREDITH, Santa Rosa. Died May 31, 1987, aged 77. Graduate of Stanford University School of Medicine, 1936. Licensed in California in 1936. Dr Kenney was a member of the Sonoma County Medical Association.

❧

KIMBALL, THEODORE S., HANFORD. Died Apr 22, 1987, aged 83. Graduate of Loma Linda University, 1929. Licensed in California in 1929. Dr Kimball was a member of the Kings County Medical Society.

❧

KUHN, RICHARD J., Redlands. Died May 7, 1987, aged 54. Graduate of Loma Linda University School of Medicine, 1959. Licensed in California in 1960. Dr Kuhn was a member of the San Bernardino County Medical Society.

LELAND, JOHN A. C., Jr, Berkeley. Died Jun 23, 1987, aged 77. Graduate of Jefferson Medical College, Philadelphia, 1936. Licensed in California in 1937. Dr Leland was a member of the Alameda-Contra Costa Medical Association.

❧

LEWIS, JACK J., Los Angeles. Died Jun 15, 1987, aged 66. Graduate of Stanford University, 1946. Licensed in California in 1946. Dr Lewis was a member of the Los Angeles County Medical Association.

❧

LINCOLN, CHARLES S., Jr., Berkeley. Died May 29, 1987, aged 62. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1943. Licensed in California in 1948. Dr Lincoln was a member of the Alameda-Contra Costa Medical Association.

❧

MAGIT, JACK R. Died Apr 1, 1987, aged 69. Graduate of University of Illinois College of Medicine, Chicago, 1941. Licensed in California in 1946. Dr Magit was a member of the Los Angeles County Medical Association.

❧

MAHANNAH, L. DUKE. Died Apr 21, 1987, aged 88. Graduate of University of Iowa College of Medicine, Iowa City, 1923. Dr Mahannah was a member of the Los Angeles County Medical Association.

❧

MUNCH, PAUL F., Santa Barbara. Died Jun 3, 1987, aged 84. Graduate of Creighton University School of Medicine, Omaha, 1935. Licensed in California in 1936. Dr Munch was a member of the Santa Barbara County Medical Society.

❧

NELSON, NORMAN B., San Jose. Died Jun 12, 1987, aged 74. Graduate of University of Southern California, 1939. Licensed in California in 1939. Dr Nelson was a member of the Santa Clara County Medical Society.

❧

NORRIS, WILLIAM J. Died Mar 27, 1987, aged 93. Graduate of Columbia University College of Physicians and Surgeons, New York, 1918. Licensed in California in 1920. Dr Norris was a member of the Los Angeles County Medical Association.

❧

PALMER, BEAN MARK. Died Apr 10, 1987, aged 87. Graduate of Medical University of South Carolina, Charleston, 1925. Licensed in California in 1932. Dr Palmer was a member of the Alameda-Contra Costa Medical Association.

❧

POWELL, TRACY O. Died Feb 12, 1987, aged 83. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1931. Licensed in California in 1932. Dr Powell was a member of the Los Angeles County Medical Association.

❧

PRITCHER, J. L. Died Mar 17, 1987, aged 90. Graduate of Kiev Medical Institute, Russia, 1921. Licensed in California in 1933. Dr Pritcher was a member of the Los Angeles County Medical Association.

❧

PURCELL, EDWARD F. Died May 20, 1987, aged 62. Graduate of Jefferson Medical College, Philadelphia, 1949. Licensed in California in 1960. Dr Purcell was a member of the Alameda-Contra Costa Medical Association.

SAMPSON, PEARL M. Died Feb 2, 1987, aged 92. Graduate of University of Colorado School of Medicine, Denver, 1926. Licensed in California in 1927. Dr Sampson was a member of the Los Angeles County Medical Association.

❧

SCHMIDT, HANS, Chico. Died Mar 29, 1987, aged 84. Dr Schmidt was a member of the Butte-Glenn Medical Society.

❧

SEGAR, LAURENCE F., Ventura. Died May 6, 1987, aged 83. Graduate of University of Michigan Medical School, Ann Arbor, 1927. Licensed in California in 1946. Dr Segar was a member of the Ventura County Medical Society.

❧

SNOOK, HAROLD. Died Apr 23, 1987, aged 89. Graduate of Loma Linda University School of Medicine, 1936. Licensed in California in 1936. Dr Snook was a member of the Los Angeles County Medical Association.

❧

SORENSEN, LOWELL E., Los Gatos. Died Jul 7, 1987, aged 57. Graduate of University of Washington School of Medicine, Seattle, 1960. Licensed in California in 1961. Dr Sorensen was a member of the Santa Clara County Medical Society.

❧

SULLIVAN, JOHN JOSEPH, Carmichael. Died Apr 16, 1987, aged 66. Graduate of Loyola University, Maywood, Ill, 1945. Licensed in California in 1950. Dr Sullivan was a member of the Sacramento-El Dorado Medical Society.

❧

TAUBE, EDWARD I. Died Apr 1, 1987, aged 81. Graduate of University of Toronto Faculty of Medicine, 1927. Licensed in California in 1945. Dr Taube was a member of the Los Angeles County Medical Association.

❧

ULICK, HERBERT. Died Feb 7, 1987, aged 50. Graduate of University of California, Irvine, 1965. Licensed in California in 1967. Dr Ulick was a member of the Los Angeles County Medical Association.

❧

WALTERS, WILLARD B. Died April 19, 1987, aged 86. Graduate of Loma Linda University School of Medicine, 1927. Dr Walters was a member of the San Bernardino County Medical Society.

❧

WILLIAMS, MALVIN J., San Diego. Died Jun 1987, aged 58. Graduate of Meharry Medical College, Nashville, Tennessee, 1956. Licensed in California in 1958. Dr Williams was a member of the San Diego County Medical Society.

New Mexico Medical Society

CIANCI, JAMES G., Albuquerque. Died Aug 16, 1987, aged 44. Graduate of University of Rochester, New York, 1969. Licensed in New Mexico in 1974. Dr Cianci was a member of the Greater Albuquerque Medical Association.

❧

MOORE, JOHN L., Roswell. Died Jul 15, 1987, aged 64. Graduate of George Washington University School of Medicine, Washington, DC, 1941. Licensed in New Mexico in 1951. Dr Moore was a member of the Chaves County Medical Society.

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

OCTOBER 1987, VOL. XLIV, NO. 10

Computers And Medicine: The Future

Marshall B. Block, M.D.

Computerization in medicine has resulted in dramatic improvements in data collection and retrieval. It has also made inroads into patient management decisions and will ultimately be utilized by physicians in word processing and decision making. For the first time because of the ability to collate large amounts of information in a short period of time, an attempt to look at the quality of medical care rendered within communities has occurred. Previous attempts have revealed interesting trends in medical care throughout the United States. As noted in previous editorials, the information that's generated from such computer searches needs to be analyzed carefully by persons who have an intimate knowledge of medicine and health care delivery in order to give meaning to such free-standing statistics.

During a recent visit to one of the intensive care units to see a patient, I was jokingly talking to a pulmonary colleague and suggested that with computers we would be able to compute "his batting average", i.e., how many patients survived that he consulted on for acute pulmonary problems. I thought that these numbers ultimately could conceivably be published in a directory to give patients a better idea of the efficacy of the physicians they choose. We laughed about the possibility of seeing a list of physicians and their "batting averages" in the local newspaper. Although far-fetched, I'm not certain such will not ultimately be available to groups who have to make decisions about cost-effective medical care delivery. It would be interesting to see whether they pick physicians who have the highest or lowest batting averages.

Likewise, information generated by computers will enable various health plans to compare their physicians to a mythical norm to see whether their physicians are utilizing services to a greater or lesser degree. They will then make decisions regarding the physician's worth to the group and will try to make changes in his behavior patterns to make him more "cost-effective." When mortality statistics from various hospitals were reported recently in the local newspapers, the hospitals greeted the information with anger and frustration. Physicians will also be faced with similar difficulties when the information that is available will be under public scrutiny.

As mentioned previously, raw statistics cannot be released but information has to be interpreted and digested beforehand. I can think of no better role for physicians than to volunteer to serve on panels which no doubt will be formulated to handle such a job. The Arizona Medical Association should play a leading role in formulating policy in concert with the other groups within the State who are involved in Peer Review. There is no doubt that intense review will reveal significant differences in how we all practice. The impact of such activity will

(Continued on page 15)

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IN THIS ISSUE

- Role of Veterans Administration Hospitals In Medical Education
  Alfred Heilbrunn, M.D.
  Louis J. Kettel, M.D., Dean
- Physicians in the News
- Arizona Supreme Court Upholds "Right to Die"
- Medi-Facts
- Inadequate
  William B. McGrath, M.D.
- New Active Members

Committee on Scientific Affairs Drafts AIDS Policy

ArMA's Committee on Scientific Affairs has responded to a directive from the Association's House of Delegates and Board of Directors — to draft an ArMA policy statement dealing with AIDS in Arizona.

The Committee's draft outline was presented to the Board of Directors for its consideration at its September 12 meeting **and the matter was tabled for further study. Following is the committee's report, but is not the official position of the Association until the Board acts.**

The committee goal was to develop a uniform policy on AIDS which can become a statewide standard, a model for individual procedures and protocols adopted by hospitals and health care facilities. It is felt a uniform statewide policy would contribute to quality care, help protect health care personnel, and establish a logical, reasonable approach for the community.

The Committee on Scientific Affairs met under the direction of committee chairman Robert Westfall, M.D., and drafted a policy which covers detection, public education, legal/insurance issues, confidentiality and treatment of AIDS. The committee's outline and ideas are as follows:

I. Detection (Testing)

A. Mandatory — only for blood, blood products, tissue and organ donors.

B. Recommended — for members of high-risk groups while they are pre-operative elective surgery patients, post-operative emergency surgery patients, or soon to receive live virus vaccinations such as varicella, smallpox, measles, rubella, mumps, oral polio or yellow fever. The committee defined high-risk groups as gay/bisexual men, IV drug users, hemophiliacs, women who are partners of bisexuals or IV drug users, and people with a history of multiple sex partners during the past eight years. Testing was also recommended for IV drug users, patients who may have sexually transmitted diseases and health care workers with needlestick or sharps parenteral exposure or mucous membrane exposure. Testing should be done immediately as a baseline and again in three months and six months. It is believed that if seroconversion has not occurred by six months, the patient will not be infected with the AIDS virus.

C. Blind prevalence studies — to determine how pervasive AIDS infection is throughout the community. Blind studies are to be conducted by the Arizona Department of Health Services (DHS) for limited periods at specified hospitals. The studies would evaluate high-risk groups and those who may have sexually transmitted diseases, and would include contact tracing.

(Continued on page 13)

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The Role of Veterans Administration Hospitals In Medical Education

The formal mission of the Veterans Administration Department of Medicine and Surgery includes patient care, education and research. Prior to 1946, there were no training programs or research and it was charged that Veterans Administration (VA) hospitals were isolated from the rest of the medical community and the care was frequently inferior. The massive return of veterans following World War II focused attention on the entire Veterans Administration. The concern raised by veteran's organizations and Congress resulted in the passage of PL 293 in January 1946. The legislation established a separate medical organization within the VA, called the Department of Medicine and Surgery, headed by a physician Chief Medical Director, with authority to conduct programs of graduate medical education. The graduate medical education programs were to be conducted in affiliation with medical schools. This was to help to provide a solution to some of the deficiencies in VA medical care programs, and at the same time significantly increase the facilities available for graduate education during the post-war period.

A policy memorandum by the first Chief Medical Director, General Paul R. Hawley on January 30, 1946 instituted the program. This memo covered the basic philosophy of the association of VA hospitals with medical schools, and outlined the division of responsibility for patient care, graduate education, training, and staff selection and appointment. Supervision of the programs was to be accomplished through Dean's Committees, a mechanism persisting today. The initial impact of the Dean's Committee came from its authority to review and approve medical staff appointments and to appoint members of the medical school faculty as part time or consultant staff to the VA hospitals.

Six months after initiation of the program in 1946, VA hospitals were affiliated with 56 medical schools and approximately 650 residents were enrolled. In 1987, 134 VA Medical Centers are affiliated with 102 medical schools, and more than 26,000 students and 27,000 residents receive part of their medical education in VA facilities.

The first students in the new University of Arizona Medical College were enrolled in the fall of 1967. At that time the Basic Sciences Building on the Health Sciences campus was completed, but there was no clinical facility. The college relied primarily on the Tucson VA Hospital as the site for clinical training and many of the clinical faculty had their original appointments at the VA.

Today, approximately one third of the required clinical clerkships are provided at the VA hospital. Residency programs are conducted in virtually every clinical discipline except Pediatrics and Ob/Gyn. In the current academic year, 77 resident stipends are paid from VA funds, over 80 residents and fellows are assigned clinical duties at the VA. Nearly all the VA physician staff hold faculty appointments, many having achieved tenure. Over a third of the VA staff is part time at the VA and part time at the medical school.

Paralleling the development of the academic clinical atmosphere has been the development of research programs at the VA. Current funding of research at Tucson exceeds one million dollars in VA funds, supplemented by funding from various other sources. Included in the research facilities are fully accredited animal laboratories and a newly constructed, unique, multidisciplinary microcirculatory laboratory.

The major impact of the VA-Medical school affiliation program nationally and locally has been twofold; for the medical school it has provided clinical material, teaching and research facilities, resources and additional staff; for the VA it has permitted the development of high quality

(Continued on page 15)

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In Memoriam

Lawrence D. Sills, D.O.

A special memorial fund has been established in the name of **Lawrence D. Sills, D.O.**, an ArMA member who was killed in the Northwest Airlines crash in Detroit August 16.

Dr. Sills was returning to his home and wife of three months, Molly, in Phoenix from Camp Tanuga in Kalkaska, Michigan. At Camp Tanuga he had fulfilled a dream by serving as camp physician at a place he had visited as a boy. His death left his wife, family members in Michigan, and friends and colleagues bereft.

A fellow physician who worked with Dr. Sills noted he was "incredibly popular with his patients," and a neighbor commented "you couldn't find a better man."

Dr. Sills, 33, was originally from Detroit. He earned his Bachelor of Science degree in psychology from the University of Michigan and his Doctor of Osteopathy degree from Michigan State University's College of Osteopathic Medicine. He interned at Phoenix General Hospital & Medical Center and in 1983 joined his medical school classmate, Brent Allen, D.O., in the practice of general and family medicine at Desert Health Associates in northeast Phoenix.

Together, Dr. Sills and Dr. Allen provided part-time professional services to a medical clinic known simply as the Southwest Clinic for a low income community in southwest Phoenix. Additionally, they helped develop the clinic as a satellite learning facility for interns from Phoenix General Hospital. They also co-wrote a publication discussing osteopathic manipulative diagnosis and therapy, and another which studied chronic pain and hypnotherapy.

A respected and dedicated physician and surgeon who had tremendous rapport with his patients, Dr. Sills was an active member of numerous professional organizations in addition to ArMA, including the American Osteopathic Association, the Arizona Osteopathic Medical Association, the American Academy of Osteopathy, the American Academy of Family Physicians, the American College of General Practitioners of Osteopathic Medicine and Surgery, the American College of Medicine and Sigma Sigma Phi, the national medical scholastic society.

Dr. Sills served as an active member of numerous hospital committees at both Phoenix General Hospital & Medical Center and Humana Hospital Desert Valley, where he had staff privileges. In addition, he was affiliated with St. Luke's Medical Center and Scottsdale Camelback Hospital.

In his memory, a special fund has been established to allow boys to attend Camp Tanuga who otherwise could not afford to do so. Donations may be sent to the Lawrence D. Sills Fund, c/o Laurence Smith, 3000 Town Center, Suite 2690, Southfield, Michigan 48075. ■

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Physicians in the News

Michael J. Krentz, M.D.

Stopping RAPE and treating AIDS are at the top of the list of "things to do" as soon as **Michael J. Krentz, M.D., F.A.C.E.P.**, is installed as president of the American College of Emergency Physicians in San Francisco next month.

Dr. Krentz, director of emergency medicine at John C. Lincoln Hospital and Health Center, Phoenix, will be installed the first week of November in the city where he completed his undergraduate college work at the University of San Francisco. But as soon as homecoming festivities are over, the workload looms.

"The first thing on the agenda is to continue the development of the image of the specialty of emergency medicine in the awareness of the public at large," Dr. Krentz said. "Emergency rooms are no longer places where people work when they can't practice elsewhere. The emergency rooms today are staffed by highly qualified specialists. When people face emergencies, we want them to think of emergency physicians, not emergency rooms."

Another important project during the year to come will be a national effort to encourage emergency physicians to get involved in organized medicine. Dr. Krentz, who personally is a member of the Arizona and the American Medical Associations, believes that emergency physicians need to join and participate in their local and national medical organizations, even though at present only about half of them are involved at the state level.

Under his leadership, ACEP will continue its Congressional lobbying efforts to prevent the inclusion of emergency room personnel in the diagnosis related group (DRG) which structures Medicare reimbursements to hospital physicians who are radiologists, anesthesiologists and pathologists (RAP). Although some political observers have pointed out that adding emergency physicians would turn RAP into RAPE, Dr. Krentz said their opposition will continue for several serious reasons.

"First of all," he said, "we don't think that DRGs should apply to the RAP group. But secondly, and more importantly, most of the patients treated by emergency physicians are not admitted to the hospital. They are treated and released. Therefore, we don't belong in any group whose primary responsibility is to treat hospitalized patients. That's not what we do in the majority of cases."

A major new project will be the establishment of a national task force to develop policies for the treatment of AIDS patients by emergency personnel.

"We have already had cases of emergency personnel, technicians, paramedics, who have refused to treat known AIDS victims. But the problem is the treatment of patients who have AIDS and don't know it. We deal with a lot of IV drug users, trauma patients and high risk types, and we need national guidelines set up on how to do it to provide the best care to the patients and protect the health care personnel."

In addition to his membership in ArMA and AMA, Dr. Krentz is a member of the Society of Critical Care Medicine and the World Association of Disease and Emergency Medical Services.

A graduate of the Medical College of Wisconsin, Milwaukee, Wisconsin, Dr. Krentz interned in surgery at Good Samaritan Hospital and Medical Center in Portland, Oregon, and spent one year in residency at Barrow Neurological Institute at St. Joseph's Hospital and Medical Center. His

(Continued on page 18)

Arizona Supreme Court Upholds "Right to Die"

The Arizona Supreme Court has handed down a landmark decision on the constitutionality of state law and medical ethics regarding the right to die, including the withholding or withdrawing of life-prolonging treatment.

Although the high court did not speak to the rights of physicians or family members to make right-to-die decisions for incompetent persons, it did reaffirm the principle that a person has the right to make that decision for himself or herself.

The court further ruled that in the event that a person is comatose or otherwise unable to make the decision personally, the decision to withdraw or withhold life-prolonging treatment (including medication, respiration, nutrition and hydration) can be made, within limits, by a court-appointed guardian. Two standards were mandated to assist the guardian: "substituted judgment," defined as reaching the decision the incapacitated person would make if he/she were able to choose, and "best interests," such as relief from suffering, preservation or restoration of functioning and the quality and extent of sustained life.

Although the court stated that the state's interest in preserving life is the most significant interest asserted, "this interest necessarily weakens and must yield to the patient's interest where treatment serves only to prolong a life inflicted with an incurable condition." In the case at hand, the high court pointed out that medical treatment would not have brought the patient out of a chronic vegetative state and into a cognitive state. Therefore, hospitalization or resuscitation would only have postponed death, rather than have improved life. Based on these observations, the court declined to hold that the state's interest in preserving life outweighed the patient's right to refuse medical treatment.

After citing the American Medical Association's policies on right to die and withholding life-prolonging treatment, the court concluded that medical ethics would not be questioned if a "do not resuscitate" or "do not hospitalize" order were placed on the chart of a patient in irreversible coma.

The court declined, however, to decide whether decisions to withhold life-prolonging treatment could be made by a physician because that was not a question in the case which came before the court. The court further declined to decide whether a family member has such authority, even though the lower court held that a family member did have such a right, because no family members were involved in the case at hand.

Copies of the Supreme Court decision or the AMA policy on withholding care may be obtained by ArMA members by contacting ArMA's headquarters, 810 West Bethany Home Road, Phoenix, Arizona 85013, (602) 246-8901 or (800) 482-3480.

Good Sam Reaches Out to Family Practice, Internal Medicine

Good Samaritan Medical Center's Departments of Medical Education and Outreach Services are offering a free medical education program and dinner at the Embassy Suites for family practice, internal medicine and general practice physicians from all parts of Arizona.

The program, "Medical Update: Diagnostics and Current Treatment," will begin at noon Friday, October 23, in the amphitheatre at Good Samaritan Medical Center, Phoenix.

Program topics include:

- Coronary angioplasty in angina and myocardial infarctions
- Cause and treatment of headaches
- New developments in GI procedures
- Trauma
- OB in rural areas
- Pancreatic transplants
- Renal transplants
- Sleep disorders

Each 25-minute topic session will be followed by a five-minute perspective.

Dinner at the Embassy Suites at 26th Street and Camelback Road, Phoenix, will be preceded by a hosted cocktail hour beginning at 6:00 p.m.

Keynote speaker at the banquet will be Edward Sattenspiel, M.D., past president of the Arizona Medical Association and chairman of ArMA's Professional Liability Committee. Dr. Sattenspiel will discuss Arizona's malpractice crisis in a speech titled "From Bad to Worse — The Medical Malpractice Crisis."

For registration information, contact Kathy Bangle at Good Samaritan's Outreach Services Department, 239-5994 in Phoenix, and 1-800-443-5972 statewide.

Early Signs of HIV Dementia

A letter to July's *Archives of Neurology* describes a series of four signs that can be used as early indicators of HIV-related dementia, a complex of neurologic disorders affecting patients with human immunodeficiency virus (HIV). Ronald S. Teschke, M.D., of the University of California-San Diego, says he noticed the signs in examinations of 40 patients with AIDS or AIDS-related complex. They are: two abnormal responses to the physician tapping certain parts of the face; slowed rapid eye movements; and difficulty repeating five numbers backward. Teschke says at least one sign is present prior to development of early HIV dementia and at least three are seen with even mild clinically apparent dementia. These signs are not unexpected, he says, since they indicate problems in parts of the brain believed involved in HIV dementia. This observation "affords the clinician a simple, rapid, easily reproducible screening examination" for the problem, he concludes.

Technological Advances In Pathology

Biosensors, a fast-developing class of medical devices, hold promise for vastly improving the analytical capability of clinical laboratories, plus allowing simple, rapid, cost-effective bedside monitoring of key biochemical indicators in hospital patients, a report in July's *Archives of Pathology and Laboratory Medicine* says. The report by Kenneth W. Hunter Jr., ScD., president of Biotronic Systems Corporation, Rockville, Maryland, is one in a series in the *Archives* detailing technical advances important to pathology. Biosensors are tiny electronic devices that use a biological molecule (antibody, enzyme, receptor) as a sensing element for such biochemical parameters as blood gases, hormones, sugars and other metabolites. Such devices have the potential to vastly improve analysis of complex biological samples in the lab and eventually allow continuous, nearly instantaneous biochemical monitoring of patients via implantable or non-invasive sensor systems, Hunter says.

AMA Sponsors Los Angeles Conference on DNA Probes

The American Medical Association will sponsor a conference, "DNA Probes in the Practice of Medicine," November 13-14, 1987, at the Bonaventure Hotel in Los Angeles.

The conference is part of a continuing series on biotechnology in medicine and is similar to one held in April in Washington, D.C. It will feature experts on DNA technology from around the country and was developed to provide clinical pathologists, microbiologists, geneticists and others with an understanding of how DNA-based diagnostics are being applied to their specialties.

Speakers will discuss the basic concepts underlying the use of DNA probes; clinical settings in which these probes will become routine; practical aspects concerning the accuracy, sensitivity and reproducibility of DNA probes in the diagnosis of genetic disorders, infectious diseases, cancer and paternity testing; and the ethical and legal issues surrounding DNA probes in screening for genetic disease.

Registration fees for the conference are $250 for AMA members, $300 for nonmembers, $125 for students and residents and $350 on-site. To register or for further information, call toll-free, 1-800-621-8335 (in Illinois, call collect, (312)-645-4987).

Radiation After Breast-Saving Cancer Surgery

While there has been a surge in interest in conservative surgical treatment—"lumpectomy"—for breast cancer patients, some surgeons question the need to follow localized excision with radiation. But a study in August's *Archives of Surgery* says postoperative radiation significantly decreases local cancer recurrence rates, reducing the need for "salvage" mastectomy. Nemetallah A. Ghossein, M.D., of the Albert Einstein College of Medicine, New York, and colleagues studied 201 breast cancer patients treated with radiation after limited surgery and followed for five years. The recurrence rate was 14 percent, less than half that reported for patients treated only by limited surgery. In another group of 324 similarly treated patients, the study says those who remained free of local recurrence or had late recurrence had significantly longer survival free of cancer that had disseminated to distant sites than those who had recurrences within five years.

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AIDS Update Conference for Arizona Medical Professionals

A one-day conference designed to update Arizona physicians on the latest information about Acquired Immune Deficiency Syndrome (AIDS) will be held Saturday, October 31, at the Westcourt in the Buttes resort, Phoenix.

Co-sponsored by ArMA, the Arizona Department of Health Services, the University of Arizona Health Education Center and Samaritan Health Service, the conference will cover both clinical and ethical issues.

The conference agenda includes an update on the status of AIDS in Arizona, clinical information about AZT and other therapeutic treatment for AIDS, case studies, a session on AIDS testing, counseling and reporting, and a review of community resources and support services for AIDS patients.

All Arizona physicians are invited to attend the conference.

Registration forms have been sent to all physicians in Arizona, but additional forms may be obtained by contacting ArMA headquarters, 1-800-482-3480 statewide, or 246-8901 in Phoenix. ■

AIDS Policy

(Continued from page 2)

II. Informed Consent/Reporting/Use of Data

A. Informed Consent — required before anyone is tested. Patients should be told there may be ramifications beyond the patient-physician relationship, the limitations of the AIDS antibody test, that results are reportable and as part of the medical record may be discovered where non-health care personnel may have access.

B. Reporting/Use of Data — should parallel DHS guidelines written to implement the law.

III. Education

A. CME AIDS-Related Seminars

B. Speakers Bureau — should be developed in cooperation between all involved medical professional organizations and DHS.

C. Counseling — should be conducted by DHS with ArMA support and should include how AIDS is spread, how it is not spread, and the importance of notifying sexual/IV drug needle partners.

D. Overall Public Education — should be aimed at high-risk groups, teenagers and conducted in cooperation with other community groups including churches and schools. It was recognized that the subject matter is difficult and sensitive, but saving lives is most important.

IV. Legal/Insurance Issues

A. Confidentiality — should be legally defined by the legislature to clarify the difference between confidentiality and anonymity, who has a right to test results, and whether separate maintenance and protection of records is necessary.

B. Insurability/Discrimination — the guidelines of the Arizona Department of Insurance on discrimination against AIDS victims were to be incorporated and patients need to be advised about legal protections against discrimination.

V. Treatment

A. Physician Responsibility to Known AIDS Patients — includes becoming educated in, and sharing the responsibility for care of, AIDS patients.

B. Abandonment — a physician who chooses **not** to treat AIDS patients is responsible for referring them to a physician who will care for them. A registry should be established of all physicians willing to treat AIDS patients.

C. Treatment — should include a wide spectrum of services available to AIDS patients, including nursing home services and housing hospice programs. ■

Portable Laser

Lasers have revolutionized ophthalmic surgery, particularly for glaucoma and cataracts, but some patients don't have access to these procedures due to age or health. Now, a case report in July's *Archives of Ophthalmology* says a portable system can make laser treatment available to these patients. Alan L. Robin, M.D., a Baltimore ophthalmologist, describes using a portable YAG laser to treat two such patients: a 95-year-old, debilitated nursing home patient with glaucoma and a 16-month-old girl with a capsule problem following cataract surgery. "Neither of these two patients could have easily undergone laser therapy with a fixed, non-portable laser," he says, noting the elderly patient was considered too ill to be moved and the child was not old enough to cooperate for a conventional procedure. Robin has also used the portable laser to treat patients in remote geographic areas.

Inadequate

William B. McGrath, M.D.

Inadequate personalities bring into adult life the unstable emotions and the unreliable judgement of puberty or the latency period.

Their traits superficially resemble those of the passive-aggressive. But the inadequate do not harbor the covert hostility of the latter. Passive-aggressives defeat us. Inadequates defeat themselves.

Also to be differentiated is failure neurosis, a neglected but still useful concept. Especially before the equal rights movement, some talented persons felt that partial failure might be safer than outstanding success. Consider the Jew outside his ghetto or the female executive or an "uppity" Negro like Martin Luther King, Jr. The wrath of the envious bigot is never far removed. Even within the family a youngster might decide to be inconspicuous in the presence of a jealous stepparent or sibling.

Back to the inadequate personality disorder. For the greater percentage we do not have glib explanations. Inadequates are not mentally defective. Few have physical stigmata (constitutionally poor habitus, incomplete secondary sexual differentiation, uncorrected overbite, etc.), and as indicators these are not reliable at all.

Suppose, however, that a child has a severe cardiac defect or a chrônic, life-threatening disease like asthma or hemophilia. Many times his very survival will depend not on himself but on the quick decisions and ministrations of others. To some extent his personality will have been patterned along lines of dependency. He could hardly be expected to learn self-reliance; in fact he had better not!

An original and warranted fear of abandonment may later dispose a person to pessimism and a kind of melancholy hypochondriasis. To admit that he was all right might interrupt your weary efforts to make him happy.

Habitually preoccupied with his own welfare, he will show little concern for yours. He will therefore hang onto that self-centeredness which is characteristic of all the personality disorders.

Or, consider, if you will, a different scenario. Mother indulges the child's every need or desire or whim. She not only indulges but anticipates his wants, and the key word is "anticipates." The lad may later suppose that anything he wants will be offered to him, and without his even having to ask. Such is the nutrient medium in which the imposter will appèar. The individual who impersonates a physician or priest or officer is demanding advantages without earning them or qualifying. (If he is motivated almost exclusively by greed he may primarily be a psychopath.) Included here are some types of "professional" veterans and disabled workmen whose whining claims for compensation and sympathy are exaggerated or fraudulent.

Inadequate personalities are the followers, the compliant, the subservient; like the so-called "groupies" of the world. They cannot resist the magnetism or charisma of their leaders. They are gullible, and respond like puppets in political and religious cults.

They look to trend setters, idols and advertisers and the media. They want guidance or models for all aspects of everyday life: child rearing, housing and transportation, styles and fashions, tastes in hobbies and music and entertainment.

On the job or managing a household or getting ready for vacation, the inadequate cannot seem to tell the difference between important and unimportant details. He or she will bog down, fussing over some nonessential item. Frequently he or she will purchase on impulse something not needed and very extravagant. Whatever it is it will be hidden at first or the actual price will not be acknowledged, and the inadequate will briefly berate himself.

These people, the inadequates, poorly tolerate being alone. They take mincing steps away from

decisiveness or self-reliance. Many of them occupy sheltered and practically anonymous little niches in bureaucracies or big organizations. Too unsure of themselves to make a serious commitment, they are likely to patronize massage parlors and porno movies.

Or they will find (or rather be found by) a domineering spouse who will make unquestioned decisions about everything that concerns them. To the inadequate it seems a lesser evil to suffer abuse than to assert himself. A striking example is the strange relationship of the prostitute to her pimp.

A pompous judge had a son with an inadequate personality. The young man spent almost eight years in college, carefully selecting courses which would not chart a way toward making a living. He is a perennial participant in group therapy where his usual platitudes are politely ignored.

He is friendless, socially awkward in spite of Arthur Murray, annoyingly eager to please. He is fretful at times but seldom either happy or sad. Any stirring of curiosity or interest is quickly crushed by his egocentricity. His father is still a personification of the whole adult world, and any hope of communication or acceptance has long since been quashed.

The maturing of the inadequate's personality was arrested in puberty. As would a child, the inadequate will abuse credit cards and be delinquent in paying bills or taxes. He will watch television until a late hour and then oversleep. Having neglected to write down the date and time of an appointment, he will be late or fail to appear.

The inadequate spends a lot of time apologizing and making excuses. Then he placates you and soothes himself with grand resolutions, taking credit as if he had actually kept them—an unlikely prospect.

These people do handicap themselves. Interviewing for a white-collar job, a chap presented himself in T-shirt and jeans and with unattractively long sideburns and dirty fingernails.

A medical school classmate was named George. While the rest of us were cramming worriedly before exams, George would be out romancing some twittery fifteen year old. After flunking, he became sales representative for a pharmaceutical manufacturer. An opportunity was arranged for him to meet the purchasing agent of a chain of drug stores. George didn't show up the first time because he had a toothache. For the second and last appointment he was half an hour late because he had taken time for another cup of coffee after breakfast.

With individuals like that, adults simply give up. Neither can we offer parents very practical advice regarding the prevention or correction of the inadequate personality disorder.

Shouted slogans are a waste of breath and so are exhortations and admonitions and threats. One obviously ought not be praised or even comforted for lack of effort or for juvenile errors of judgement.

If the reader will gloss over the sexual innuendo, there is an apt metaphor: You cannot push a wagon with a rope. The old principles of reward and punishment are after-the-fact, and they usually don't work. For they inadvertently reinforce the young person's mirrored preoccupation with the consequences of his behavior—but only as it relates to himself!

Were we to submit a hundred illustrations of the inadequate (or any other) personality disorder, the most common flaw would still be lack of consideration for others.

There is too much emphasis nowadays on building up the individual's self-respect. Never mind that. Emerging from the egocentricity of childhood a person needs most of all to learn respect for others.

What beckons the individual most beguilingly toward growing up are parental expectations, clearly conveyed and with a minimum of moralizing.

During the latency period it is probably wiser to emphasize good manners than morals. In the long run manners and morals do converge in that most profound of all injunctions: Do unto others . . . ■

William B. McGrath, M.D.

Editor's Message

(Continued from page 1)

not only be felt in our offices, but have a staggering impact on the future development of medical service within our State. ■

Marshall B. Block, M.D., Editor

VA Hospitals

(Continued from page 4)

patient care programs which would have been impossible without the support of the medical schools.

As we approach the 20th anniversary of the affiliation between the University of Arizona College of Medicine and VA Medical Center in Tucson, it must be judged a resounding success. ■

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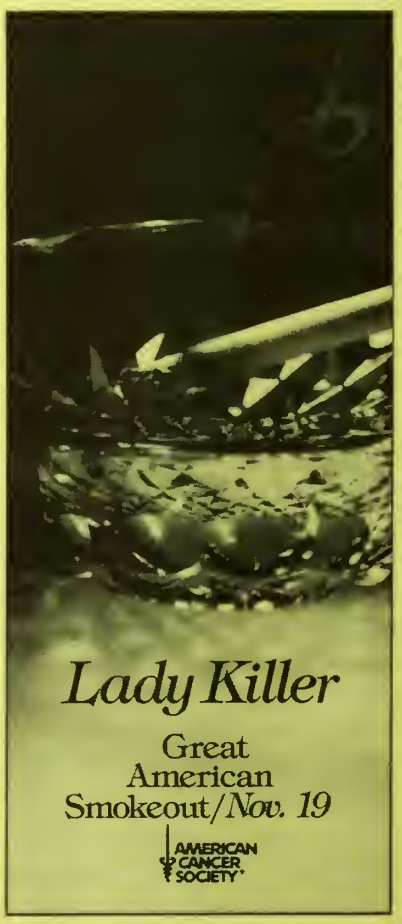

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Dr. Krentz

(Continued from page 9)

interest in emergency medicine grew during that time and he spent the next two years serving as emergency physician at St. Joseph's and at Lincoln. In 1977 he became Director of Emergency Medicine at Lincoln.

Dr. Krentz has been a member of the ACEP Board since 1984 and has served as chairman of its Long Range Planning Committee and its Emergency Medical Services Committee. In addition, he is a past president of the Arizona Chapter ACEP, where he also served as councillor and board member.

The American College of Emergency Physicians is the thirteenth largest specialty society in the United States with more than 11,200 members in the U.S., Canada and Puerto Rico. Its primary goal is to improve the quality of emergency medical care by providing continuing education for its membership and educating the public on ways to access emergency medical care and how to prevent medical emergencies.

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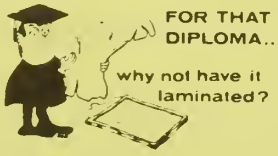

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Mapping Approaches to Gene Identification in Humans

Presented as the Kroc Foundation Lectureship before the Western Association of Physicians in Carmel, California, February 3, 1987

RAYMOND L. WHITE, PhD; JEAN-MARC LALOUEL, MD, ScD; G. MARK LATHROP, PhD; MARK F. LEPPERT, PhD; YUSUKE NAKAMURA, MD, *and* PETER O'CONNELL, PhD, *Salt Lake City*

Although a number of human genes that cause disease have been traced through the defective product, most genetic defects are recognized only by phenotype. When the biochemical defect is unknown, a gene can be located only through molecular approaches based on coinheritance (genetic linkage) of the disease phenotype with a particular allele of a polymorphic DNA marker that has already been mapped to a specific chromosomal region. Linkage studies in affected families have already localized genes for several important diseases, including cystic fibrosis. Finding a genetic linkage in families in which a disease segregates requires that the human genetic map have a large number of polymorphic markers; when the map is dense enough, any disease gene can be located by linkage to a known marker. Many DNA segments with a high degree of polymorphism are being found and mapped as markers in normal reference pedigrees. Genetic linkage mapping has implications even broader than its application to prenatal diagnosis or therapeutic strategy; analyzing mutations in important genes will illuminate basic mechanisms in molecular biology and the early events that lead to cancer and other disorders.

(White RL, Lalouel JM, Lathrop GM, et al: Mapping approaches to gene identification in humans. West J Med 1987 Oct; 147:423-427)

EDITOR'S NOTE: *The following article was invited because its topic is critical and current. Gene identification promises to alter the practice of medicine and will do so within the professional lifetimes of many who read the* JOURNAL. *Dr White and colleagues tell us why, how, when and where.*

Molecular genetics and medicine have formed a natural partnership, each making a significant contribution to and drawing from the other. For example, insulin, growth hormone, factor VIII protein and tissue plasminogen activator, made directly from human genes cloned in *Escherichia coli*, are already playing an important role in clinical medicine. The identification and cloning of additional human genes is key to expanding this approach to produce other therapeutic agents.

Molecular genetics is also beginning to have an impact on the diagnosis of rare genetic disorders. To provide counseling information to parents, DNA technology can often be used to diagnose in utero cystic fibrosis, sickle cell disease and thalassemia, Duchenne muscular dystrophy, Huntington's disease and a number of other disorders.

The analysis of mutations that have been found in important genes within the human population has made significant contributions to our understanding of basic mechanisms in molecular genetics and biology. For example, the insights gained by Brown and Goldstein into the mechanisms of receptor-mediated endocytosis[1] were made possible largely by the identification of a number of different mutant alleles of the low-density-lipoprotein (LDL) receptor gene. We expect that careful identification of phenotypes in a large population will continue to contribute fundamental concepts to molecular biology. Nathans and co-workers recently characterized the genetic basis of color vision[2] by taking advantage of the wealth of different alleles that have been ascertained in humans.

The applications described above, however, require a cloned gene as a basic working tool. The direct approaches that have been so effective in cloning those genes for which we have some biochemical knowledge are not effective in approaching the great majority of genes defined by the McKusick catalog of human genetic disorders, as they have not yet yielded biochemical clues. Our objective, therefore, is to develop new methods to identify and to clone intriguing genes whose defective product has not been identified.

The Linkage Approach to Gene Identification and Cloning

Our approach is based on a new paradigm of gene cloning: through determination of a precise location for a gene on a chromosomal map, it will be possible to identify the gene for cloning. Is the paradigm realistic? It has already succeeded; within the past year, the genes for three diseases—chronic granulomatous disease,[3] Duchenne muscular dystrophy[4] and retinoblastoma[5]—have been cloned by means of a strategy that depended initially on determining their map location. In all three cases, deletions identified in the DNA of affected persons had also been crucial to the initial gene localizations; these deletions made it possible to identify candidate genes whose involvement in the disease could ultimately be shown.

From the Department of Human Genetics, Howard Hughes Medical Institute, University of Utah School of Medicine, Salt Lake City.
Reprint requests to Raymond L. White, PhD, Howard Hughes Medical Institute, University of Utah, 701 Wintrobe Bldg, Rm 631, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

CEPH = Centre d'Étude du Polymorphisme Humain
cM = centimorgan
LDL = low-density-lipoprotein
VNTR = variation in the number of tandem repeats

Before deletions that are associated with a defective gene can be found, however, the search must be narrowed to a particular chromosomal region. The approach to localization we have taken is that of genetic linkage in family studies: we use genetic markers to follow the inheritance of various chromosomal segments. As indicated in Figure 1, if the gene causing a disease is located within one of the marked regions, there will be a correlation between inheritance of the disease and inheritance of one or more markers on that chromosomal region. If the correlation is sufficiently strong, it serves to map the disease gene to a specific region of a specific chromosome.

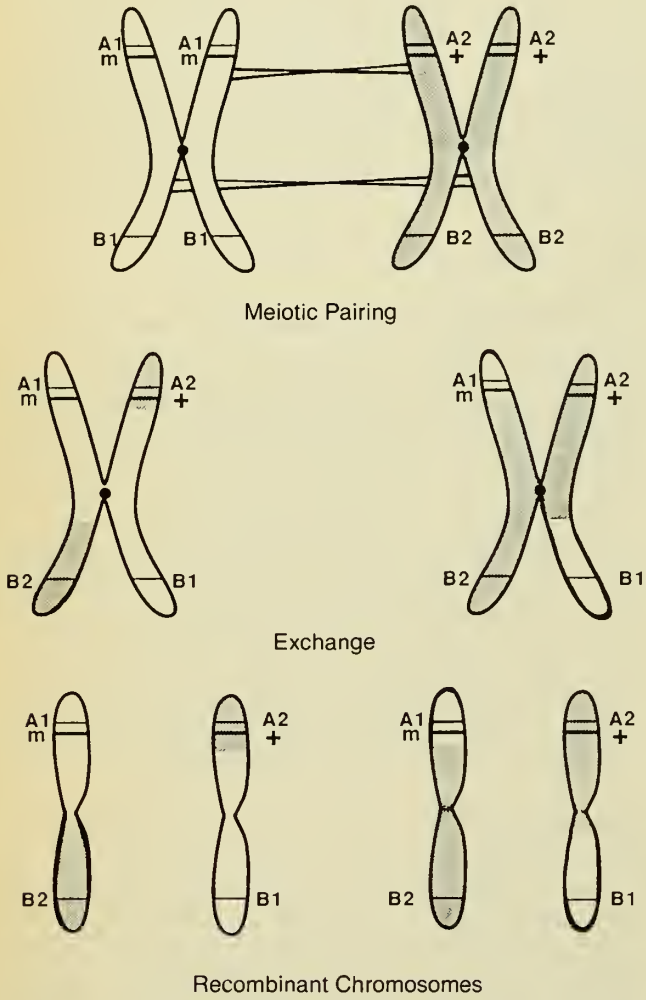

Figure 1.—This illustration of genetic linkage shows products of meiosis, which are single recombinant chromosomes consisting of a mosaic of segments from the four chromatids of each set of homologous chromosomes in a parent. In this example, A and B are marker loci, each with two alleles (the parent is heterozygous for both markers). A gene associated with a disease that is segregating in the family is mutant **(m)** on one chromosome (shown in white) and wild-type **(+)** on its homologue (gray). The two breakpoints shown fail to separate the disease gene from the linked marker A during meiotic exchange, so that in the recombinant progeny chromosomes, the A1 allele will appear in all affected persons in the family. This correlation serves to establish the chromosomal location of the previously unmapped disease gene.

Genetic Marker Systems

The genetic markers used in linkage studies are based on DNA sequence polymorphisms—variations in DNA sequence that exist within the human population. DNA sequence polymorphisms seem usually to have no effect on gene activities, but they do serve to mark the region of the chromosome within which they reside. Many of these DNA sequence variations affect the length of the DNA fragments produced by cleavage with bacterial restriction enzymes; the fragments of different sizes (alleles) can be detected by hybridization with DNA probes by the method of Southern.

Good markers are critical to the success of linkage approaches. Because families with a specific genetic disease are relatively uncommon, it is important to obtain as much information as possible from each family. Therefore, the marker systems need to have many alleles so that almost all persons in a population will be heterozygous. This degree of heterozygosity can be difficult to obtain when the DNA sequence variation reflects simple base-pair changes that affect restriction sites, but another class of DNA sequence polymorphism has come to the fore as a rich source of highly informative markers.

As indicated in Figure 2, some DNA sequence variants are the result of variation in the number of tandem repeats (VNTR) of an oligonucleotide sequence at a locus. This type of variation means that there can be, and often are, many possible lengths for the restriction fragment that carries the VNTR locus. By extension of a protocol developed by Jeffreys and associates,[6] Nakamura in our group has now identified a large set of new VNTR loci (Table 1). In brief, genomic clones that contain tandemly repeated sequences ("minisatellite" regions) are identified with oligonucleotide probes

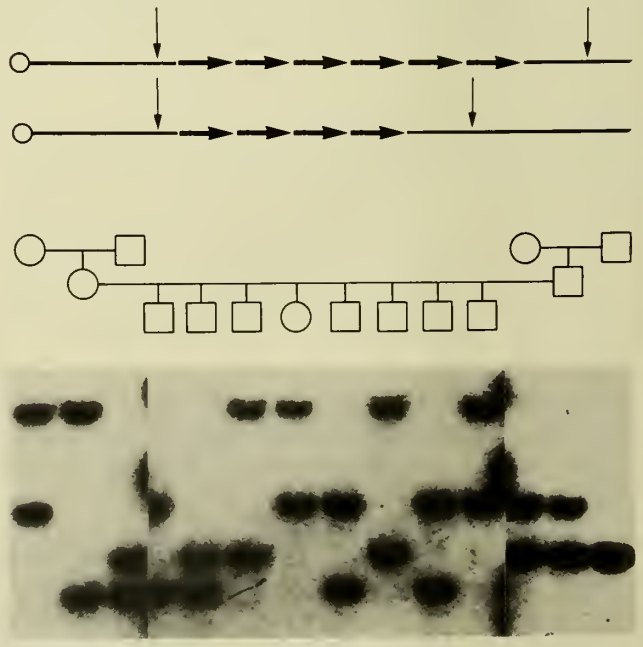

Figure 2.—The autoradiograph shows how variation in the number of tandem base repeats at the Harvey*ras*-1 locus on chromosome 11 has generated a four-allele system within a three-generation family. Each lane contains DNA from the person represented in the pedigree symbol directly above it. **Top,** Vertical arrows indicate cleavage sites for the enzyme *Taq*I, showing how a larger number of tandem repeats will lengthen a restriction fragment and account for the differences in molecular weight reflected in the electrophoretic mobility of the fragments on the gel (from White et al,[8] reprinted by permission from *Nature,* © 1985 Macmillan Journals Ltd).

based on the sequences of known variation in the number of tandem repeats at several different loci. These genomic clones are then used to probe DNA from unrelated people to determine whether the cloned fragments hybridize with VNTR loci. Many do, and more than 100 new VNTR loci have now been detected. Several of these have been sequenced; as indicated in Table 2, there are two classes of sequence similarity. The GNNNGTGGG sequence, conserved across VNTR loci that have not been ascertained by the same oligonucleotide,[7] may well have functional significance. Additional similarities within sets having some, but not complete, homology to a particular oligonucleotide suggest common historical or evolutionary roots for these systems. We believe that it will now be possible to identify a number of new VNTR loci based on direct detection with synthetic oligonucleotide probes that are variants on these thematic sequences.

We expect highly polymorphic VNTR loci to be especially important in mapping genetic disease loci in those circumstances where family resources are limiting. In addition, because we estimate that several thousand such loci exist in the human genome, they could form the basis for a high-resolution map, at the level of 1 centimorgan (cM, representing about a million base pairs) that could be very useful in the development of a physical map consisting of overlapping cloned segments. Such maps would accelerate the progress of the venture to sequence the human genome. The special feature offered by the 1-cM linkage map is that it would serve to group and to order clusters of cloned DNA segments over distances from 1 megabase or less—the upper limit of resolution of the large restriction fragments separated by pulse-field gel electrophoresis—to entire chromosomes.

Genetic Maps

Primary maps have been developed for the human X chromosome, chromosome 12, chromosome 13 and segments of chromosomes 6 and 11 (Figure 3).[9-11] The maps consist of marker loci spaced at intervals representing recombination fractions of 0.2 or a little more—that is, the two loci delineating each interval segregate separately less than about 20% of the time. Markers at this level of spacing should detect any disease gene located within the mapped segment, if adequate family materials are available.

We now have a data base of more than 60 normal families in which to follow the inheritance of markers for the mapping project. These families were chosen because they were ideal in structure for linkage mapping: each had four living grandparents and a large sibship. We expect the resource of the linkage families to become increasingly useful in the primary localization of new genes. Even at this early stage in the development of the data base, we have been able to link almost two thirds of a set of 28 new marker systems to markers already present in the data base; 20 of these linkages

TABLE 1.—*Summary of Screening for Variation in the Number of Tandem Repeats (VNTR) Polymorphism**†

Source of Oligonucleotide Sequence	*Positive Clones per Genome*	*Clones Tested for Polymorphism*	*VNTR Polymorphism*	*Percent‡*	*Site Polymorphism§*
Zetaglobin	180	57	12	21	20 (6)
Insulin	220	20	4	20	8 (1)
Myoglobin-1	150	65	8	12	19 (8)
Myoglobin-2	18	18	8	44	8 (2)
HBV-1	200	75	13	17	38 (13)
HBV-2	40	15	2	13	10 (3)
HBV DR 1	50	26	6	23	6 (2)
HBV DR 2 and 3	150	58	15	26	40 (19)
YNZ22	38	38	9	24	25 (11)
Totals		372	77	21	174 (65)

*We screened 1 genomic equivalent (almost 75,000 colonies) to 2 genomic equivalents for each probe. The number of positive clones per genome means the number per 75,000 colonies.

†From Nakamura et al,[7] reprinted by permission, ©1987 American Association for the Advancement of Sciences.

‡The proportion of VNTR DNA markers among the tested cosmids.

§The numbers in parentheses represent the number of cosmids that showed site polymorphisms with two or more restriction enzymes.

TABLE 2.—*Comparison of the Core DNA Sequences of Variation in the Number of Tandem Repeats Loci**

Zetaglobin	GGTTGTGAGTGGGGCACA (9G; 2C/18 nucleotides)
YNZ2	GAGGCTCATGGGGCACA (7G; 4C/17)
YNZ22	TGGAGTCTCTGGGTGTCGTGCGTCAGAGT (12G; 5C/29)
YNZ132	TGCAGGCTGTGGGTGTGATGGGTGA (13G; 2C/25)
Insulin	ACAGGGGTGTGGGG (9G; 1C/14)
YNI10	CTGGGGGTGTGGGTGCTGCTCCAGGCTGTCAGATGCTCAC (16G; 10C/40)
THH59	CTGGGGAGCCTGGGGACTTTCCACACC (9G; 9C/27)
YNH24	CAGGAGCAGTGGGAAGTACAGTGGGGTTGTT (14G; 3C/31)
Myoglobin	CTAAAGCTGGAGGTGGGCAGGAACGACCGAGGT (14G; 6C/33)
Common sequence	GGGNNGTGGGG

*Adapted by permission from Nakamura et al,[7] ©1987 American Association for the Advancement of Sciences.

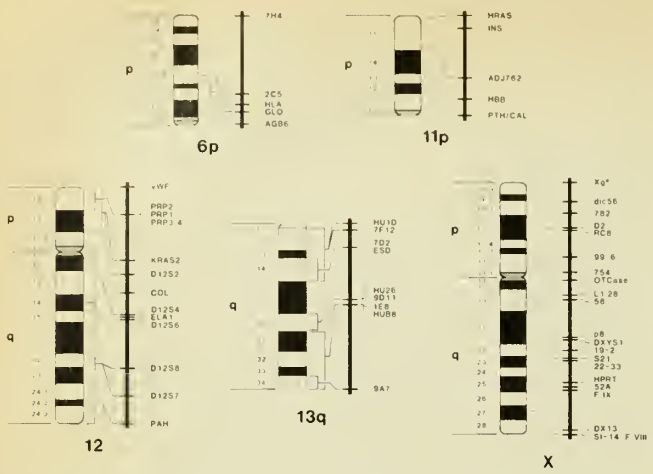

Figure 3.—The primary linkage maps are of five human chromosomes. Genetic distances between markers are based on combined male and female meioses. Physical locations on the chromosomes are indicated for selected markers. (Adapted from Leppert et al,[9] Drayna and White[10] and Leach et al.[11])

have resulted in new chromosomal localizations. Of course, as each new set of markers is linked in, the data base becomes more powerful as a primary mapping tool. To increase the usefulness of the data base, an international collaboration has been encouraged by the Centre d'Étude du Polymorphisme Humain (CEPH) in Paris. Investigators wishing to join in the collaboration receive DNA from cell lines derived from most of the reference families from Utah, as well as from several other sources, and agree to supply the primary genotypic data that they collect to CEPH for the use of other researchers. Within a few years, a very precise localization for any newly isolated gene should be possible through linkage with the CEPH DNA panel.

The LINKAGE[12] computer software makes it possible to compare the recombination frequencies obtained from female meioses with those from male meioses. Previous reports[13] led us to expect a modestly increased recombination frequency in women relative to men; the observations have been somewhat surprising, however.

The differences are most easily expressed in ratios of map distance as determined by the LINKAGE programs.[12] For chromosome 13, the ratio of female to male map distance is 3.89[9]; no significant improvement in likelihood for the estimate of map distance as a function of recombination frequency is achieved by allowing this ratio to vary among the intervals. In contrast, the result obtained for a segment of the short arm of chromosome 11 indicates that the ratio of female to male map distance can vary significantly between adjacent intervals (T. Holm, P. O'Connell, M. Leppert, et al, unpublished data, October 1986). Furthermore, the more distal segment of chromosome 11p gives a higher frequency of recombination in men than in women, the reverse of what was found on chromosome 13. The more proximal segment of 11p shows an almost equal frequency of recombination in males and females. Each of these differences in sex-specific map distance differs significantly from the other. Two conclusions follow from these findings: first, two genetic linkage maps for humans need to be constructed, one reflecting female map distances and the other male map distances. Second, the relationship of recombination frequency to physical distance must be heterogeneous in either male or female meioses or, more likely, in both.

Mapping Disease Genes

Cystic Fibrosis

The initial localization last year of the gene for cystic fibrosis to the long arm of chromosome 7 spurred a cooperative effort among several laboratories to refine the map distances between the two markers most closely linked to cystic fibrosis and to develop better estimates of the relative order of the marker loci with respect to the cystic fibrosis gene.[14] Several new markers have recently been tested in a large number of cystic fibrosis families. In addition, the marker-marker relationships have been more precisely defined by linkage analysis in our large reference panel of normal families. In support of the initial report of the collaborators, there is now strong evidence that the cystic fibrosis gene is located between the D7S8 and MET marker loci, with odds greater than 10,000 to 1 favoring this location with respect to the next most likely location.[15] These markers now serve to physically define a region within which the cystic fibrosis gene must lie and provide the basis for accurate diagnostic tests.

Given the genetic evidence favoring a physical proximity for the marker loci, we expected to be able to locate at least some of our marker loci on the same large restriction fragment using pulse-field gel technology. We have been disappointed in this endeavor, however; no two of our markers have yet been found to map to a common fragment. This finding raises some concern, but certainly does not yet establish, that the region spanned by the markers may be somewhat larger than was originally estimated based on the average estimate of 1% recombination—that is, 1,000,000 base pairs.

Several approaches to identifying the cystic fibrosis gene are now possible. It is certainly worthwhile to try to develop cloned DNA segments from the region spanned by the markers. Such clones can be used to screen DNA from persons with cystic fibrosis in an attempt to detect possible deletions in the gene. As mentioned earlier, deletions have proved valuable in isolating the genes responsible for Duchenne muscular dystrophy, chronic granulomatous disease and retinoblastoma. Deletions at the cystic fibrosis locus, however, may not be frequent and other tests of genes from this region will need to be devised, presumably using functional assays based on correction of the chloride ion channel defect.[16,17]

X-Linked Spastic Paraplegia

The genetics of spastic paraplegia are characterized by both autosomal and X-linked inheritance. Furthermore, there may actually be two forms of the disease, a pure form and a complicated form presenting with a variety of additional features that sometimes include severe mental retardation. We recently reported a study of an extended kindred with the simple form of spastic paraplegia showing linkage to several markers on the X chromosome.[18] Our screen of X-chromosome markers in this family yielded significant evidence of linkage between two markers, S21 and YNH3, and the disease. Previous mapping of the X chromosome[10] located marker S21 in the middle of the long arm. Although the normal map is not well resolved as yet in this region, the LOD scores—logarithm of the odds favoring linkage between a DNA marker and the clinical phenotype—of over 4 for linkage of spastic paraplegia in this family to S21, YNH3 and nearby markers provided strong support for localization of the gene.

It was of interest, therefore, that another recent report[19]

had shown linkage of a gene for spastic paraplegia in a family in which the complicated form of the disease segregates to a different pair of markers—ST14 and DX13, located at the distal end of the long arm of the X chromosome. Analysis indicated that the likelihood that the spastic paraplegia loci differ in the two families is significant[20]; this result was obtained by comparing the likelihood of the observed data under the model of a single locus with the likelihood of the observed data under the model of two loci.

We conclude that there are at least two loci on the X chromosome that can cause spastic paraplegia, and this likely accounts for the heterogeneity that has been suspected on clinical grounds. This distinction will be important to counselors in providing information to families at risk. It also provides an especially clear example of the value of genetic analysis for resolving complex and heterogeneous phenotypes, in this case indicating a genetic basis for apparent clinical heterogeneity. By contrast, although there is significant clinical heterogeneity in cystic fibrosis, the great majority of cystic fibrosis cases result from genetic lesions at the same locus on chromosome 7.

The Future of Genetic Mapping in Medicine

Over the next several years a number of important genetic disease loci will be mapped by linkage and cloned. Many of them will have important scientific implications. Characterization of the gene causing familial polyposis coli, for example, will almost certainly provide profound new insights into early events in the genetic pathway leading to colon carcinoma. Similarly, the gene for ataxia telangiectasia is likely to be found soon and will provide new information on the genetic cause of the early stages of lymphoma. Genes for neurofibromatosis, important muscular dystrophies, neurologic disorders and developmental defects should all be identified by the linkage approach, generating important new experimental tools for investigating these defects. The limiting feature now would seem to be the family materials: can we locate affected families that are large enough to provide a significant statistical signal?

We may soon be able to identify alleles in the human population that predispose to common diseases, such as coronary artery disease, cancer, diabetes mellitus and bipolar mental illness. The increased relative risk for these disorders that has been observed in some families may be due to segregation of a gene that increases the likelihood of disease. For example, a variant apolipoprotein B gene might produce a gene product with reduced affinity for the LDL receptor, resulting in high levels of LDL cholesterol and an increased risk of coronary artery disease. If such variants exist, the technology of molecular genetics will permit their detection. Familial components, however, are not necessarily identical with genetic components; annual income and tuberculosis each can be shown to have a strong familial component, presumably not due to genetic inheritance. One of the major opportunities provided by rigorous genetic approaches will likely be to show which factors are genetic and which are not so that appropriate therapeutic strategies can be defined. The partnership of clinical medicine and molecular biology thus comes full circle in the form of a challenge for DNA technologists to develop cheaper and more efficient means of determining the genotypes of persons to be able to respond to the possibility of identifying those at risk for common diseases and to the need for isolating and cloning of known genes for rare but devastating disorders.

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Clinical Medicine

Patterns of Cervical Spine Injury and Their Associated Lesions

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Motorcycle riding and diving into shallow water continue to present a high risk of cervical spine injury, often complicated by spinal cord damage. In patients with high cervical cord trauma, differentiation of arterial hypotension due to losing vasomotor control from the effects of internal hemorrhage can cause difficulty. In a series of 123 consecutive cases of cervical spine injury, no evidence was found that either early surgical treatment or steroid administration exert a favorable influence on recovery from traumatic myelopathy. When compared with other series, differences were found in the nature, frequency and severity of both spinal and associated injuries, resulting from the relative frequency among the population studied of trauma due to a particular mechanism—traffic accident, diving, industrial injury—and the special functions and location of the hospital from which information is gathered.

(Guthkelch AN, Fleischer AS: Patterns of cervical spine injury and their associated lesions. West J Med 1987 Oct; 147:428-431)

Cervical spine trauma represents an important cause of mortality and morbidity, particularly in young people. Over the years the clinical features of several large series of cases have been reported from both the United States[1-5] and other countries.[6-8] In this article we review our experience with patients with this injury admitted to our service during a six-year period and compare our findings with others recently reported, identifying some features of the injury that remain relatively constant between series and others, such as the incidence of associated injuries, that are more variable.[7,9-12]

Patients and Methods

We examined the records of 148 patients admitted to the University of Arizona Health Sciences Center between January 1, 1980, and December 31, 1985, in whom a tentative diagnosis of acute injury to the cervical spine or spinal cord had been made. Whenever there was a discrepancy between the initial and final radiologic diagnoses, the original films were reviewed with a radiologist. Excluded were 23 patients suffering only from an uncomplicated ligamentous strain and 2 patients having generalized metastatic disease who presented with neck pain due to pathologic fracture of the cervical spine without a clear history of trauma.

The remaining 123 patients were divided into two groups according to the severity of their spinal injury. Considered as major injuries were all those that required hospital admission, including all instances of neurologic deficit and those that required the application of halo traction or other immediate surgical treatment. Patients with minor injuries were those needing no more treatment than the application of a Philadelphia collar, having no neurologic complications and admitted to hospital because of associated injuries or pending an appropriate disposition.

Six categories of major associated injury were established for each group: intracranial damage, other skull or facial fractures, injuries to the rest of the spinal column, rib fractures and intrathoracic injuries, intra-abdominal and pelvic visceral lesions and limb injuries with fractures or neurovascular lesions (or both). All other associated injuries were regarded as minor.

Statistical comparisons of the ages of subjects were made using the Mann-Whitney nonparametric test. Other comparisons were made using the χ^2 test. For simplicity, only the P values resulting from these tests are shown.

Results

General Features

Of the 123 patients, 97 were male (79%) and 26 female (21%), having an age range of 5 to 83 years and a median age of 26 years (mean 30 years). A total of 93 patients (76%) suffered major cervical spine injuries as previously defined, and there were 30 (24%) minor cervical injuries. The median hospital stay of all patients was 8 days (mean 14 days); 6 (5%) died in the hospital, 19 (15%) were transferred to skilled or intermediate care facilities and 98 (80%) returned home.

Etiology

Most patients (100/123; 81%) were injured as a result of traffic accidents. Of 91 cases in which adequate details of the accident were given, 11 (12%) occurred to persons riding motorcycles (10 drivers and 1 passenger) and 5 (5%) to pedestrians. Two patients received additional injuries when assaulted by a person traveling in another involved vehicle!

Falls from a building (or scaffold) accounted for six injuries (5% of the whole series) and there were two industrial accidents. Three adults (2%) suffered gunshot wounds. Of nine patients injured during sports, seven (6%) were injured while diving or jumping into swimming pools, one was a boy who headed the ball while playing soccer and one was thrown while wrestling.

Nature of spinal injury. The levels of fracture or dislocation in the cases of major cervical injury are shown in Table 1.

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The minor cervical injuries included various degrees of undisplaced fracture through a lamina or of the anterior margin of a vertebral body and fractures of transverse or spinous processes.

A cervical spinal cord injury occurred in 27 patients (22% of the whole series; 28% of those with major cervical lesions), the injury being complete or almost complete in 13 cases (48% of those with cord damage); the frequencies of the various neurologic syndromes are shown in Table 2. In two instances patients with cord lesions had evidence of nerve root damage as well, while five patients—5% of major injuries—sustained a traumatic radiculopathy without myelopathy. Among the major cervical spinal injuries, spinal cord damage was significantly ($P<.01$) more frequent in the patients suffering subluxations or dislocations of the cervical spine (17/34; 50%) than in those with fracture alone (7/56; 13%). It was also significantly more frequent ($P<.001$) in patients whose bony injury lay between C-5 and C-7 (20/49 cases; 41%) than in those with bony injuries between C-1 and C-4 (4/41 cases; 10%). The difference between the ages of the patients who did (mean 30 years) and did not (mean 31 years) suffer a spinal cord injury was not significant ($P=.6$, Mann-Whitney).

The two youngest patients in this series, aged 5 and 16 years, both sustained spinal cord injuries without radiologic abnormality.[13] One previously asymptomatic 56-year-old patient having severe spondylosis with spinal stenosis sustained a hyperextension injury without fracture or dislocation but with temporary quadriparesis.

Associated injuries. Associated injuries were recorded in 79/123 (64%) of patients, comprising 55/93 (59%) of those who had sustained major cervical spine injuries and 24/30 (80%) of those with minor cervical injuries.

TABLE 1.—*Frequencies and Levels of Fractures and Dislocations (Including Subluxations) With or Without Spinal Cord Damage**

Level of Fracture	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*
Major fractures without dislocation, N=56							
Fractures, No.	14	15	5	8	21	20	14
With cord damage, No.	0	0	0	1	4	2	0
Minor fractures, N=30							
Fractures, No.	0	2	4	0	7	11	13
Level of Dislocation		*C1-2*	*C2-3*	*C3-4*	*C4-5*	*C5-6*	*C6-7*
Dislocations, N=34							
Dislocations, No.		7	1	3	6	8	9
With cord damage		1	1	1	4	4	6

*3 patients had spinal cord lesions without radiologic evidence of fracture or dislocation.

TABLE 2.—*Segmental Levels and Frequencies of Syndromes of Spinal Cord Damage**

	Spinal Cord Level	
Cord Damage	*C1-4*	*C5-7*
Complete lesions	2	11
Anterior cord syndromes	1	1
Central cord syndromes	2	4
Brown-Séquard syndrome	3	1
Concussion	..	2
Total	8	19

*In 3 patients the upper neurologic level was slightly higher than the level of bony injury.

In our series, unlike that reported by Reiss and coworkers,[10] there was no significant difference ($P=.175$, Mann-Whitney) between the ages of the patients who did (mean 32 years) and who did not (mean 28 years) sustain an associated injury, nor was there any difference in the incidence of associated injuries between the patients with spinal cord damage (52%) and those without this complication (49%; $P<.6$). More of the patients injured in traffic accidents sustained associated injuries (67/100; 67%) than did those injured in other ways (11/23; 48%). The difference, however, is not formally significant ($.1>P>.05$) and is much less striking than that recorded by Soderstrom and associates,[11] namely, 36% versus 10%.

There were 11 instances of trauma to other parts of the spinal column: 7 of these involved the thoracic spine, 2 of them being complicated by paraplegia; 3 were lumbar fractures and 1 a fracture of the sacrum.

Neither the subsequent clinical histories of the patients nor the autopsy findings in the fatal cases evidenced any major associated injuries beyond those recorded at the time of admission. One negative emergency laparotomy, however, was done for a moribund patient, regarded as in "shock," who later proved to have a complete cord transection due to a dislocation at C1-2. On a second occasion, which occurred after the conclusion of this series, a negative laparotomy was done on a patient admitted with a high cervical cord lesion who had a mean arterial pressure of 50 torr. In this case peritoneal lavage had disclosed a borderline erythrocyte count.

Management

The treatment of this series of patients followed the usual lines. In most cases a cervical collar had been applied by paramedical personnel at the scene of the injury. The patients were immediately assessed by a member of the trauma service, resuscitation was commenced and a neurosurgical consultation was done; a few gravely injured persons were transferred immediately to the operating room. All the patients who were in shock or having evidence of spinal cord damage received steroids, usually about 100 mg per day of methylprednisolone sodium succinate or an equivalent, for two to four days. We found no indication that any particular regimen of steroid therapy was associated with more or less recovery of cord function than the others.

In all, 66 patients (71% of those with major cervical spine injuries) were initially managed by skeletal traction; of these, 19 (29% of those so treated) later required fusion. Immediate intervention—reducing locked facets, decompressing depressed laminar fractures, removing extruded bony or disc material—was required in 11 cases (12% of major injuries) and elective early cervical fusion was undertaken in 11 patients. Four patients having stable fractures of the lateral mass of the atlas, one with a stable fracture of the odontoid, one with a compression fracture of the body of C-7 and two of the three with gunshot wounds, were electively treated by applying a Philadelphia collar. Two patients admitted to the hospital in extremis died before definitive treatment of their cervical spine lesions could be instituted.

Of the 25 nonmoribund patients having spinal cord damage, 13 were treated by halo traction alone and 12 by spinal fusion, with decompression in two cases. There was no difference in the eventual degree of return of neurologic function between the two groups.

Discussion

Cause and Diagnosis

A comparison of the demographic, etiologic and diagnostic details of the patients in our series with those of three other series collected in the US in recent years is shown in Table 3. Although these series are not wholly comparable as one of them somewhat antedates the others and relates only to patients with spinal cord damage,[4] they have many similarities, some, but not all, of which they share with earlier studies and those from other countries. This suggests that the characteristics of the traumatic lesions of the cervical spine are determined by more than one set of factors, one of which remains constant between series, while the others vary.

Anatomic considerations. Despite great differences in the conditions responsible for cervical spine injuries—such as the speed of motor traffic—over the past 60 years, the frequency distribution of the vertebrae involved in our cases of major fracture of the cervical spine (Table 1) is very similar to that reported by Jefferson in 1925.[14] He noted that the most common site of fractures of the cervical spine was toward its lower end, but predicted from indications in his own data that a second peak would be found at C1-2. These two peak frequencies have since been identified in other series,[1,2,5] as well as in our own.

Spinal cord damage is found significantly less often in patients with lesions at C1-2 than in those with lower cervical damage. Bohlman noted cord damage in only 11/69 patients with lesions at C1-2 but in 167/229 of those with lesions at C-3 to C-7 ($P < .001$).[3] In our series the proportions were 2/26 for C1-2 lesions and 22/63 for major injuries at C-3 to C-7 ($P < .01$). This may reflect a combination of two factors. On the one hand complete cord lesions at this level are often immediately fatal, but also the spinal canal is relatively wide in relation to the diameter of the spinal cord, so that only cases with gross displacement of the vertebrae—implying very severe trauma—suffer cord damage.

The frequency distribution of the minor fractures of the cervical spine differs significantly (degrees of freedom = 6, $P = .02$) from that of the major fractures, showing no peak at the upper end of the spine. This may be because many of these were avulsion injuries of the transverse and spinous processes, associated with trauma to the upper limb girdle. The statistically significantly ($P < .05$) increased incidence of trauma to other systems in cases of minor compared with major cervical injury might appear paradoxic. It probably merely indicates that few patients who have sustained minor neck trauma without other injuries are admitted to hospital.

Epidemiologic features. Cervical spine injuries largely affect young people: in four recent North American series (Table 3) and in one from Australia,[6] the median age of the victims was 25 years with mean ages between 28 and 35 years, while in Whitley and Forsyth's[5] series the mean age was 31 years. In all these, male victims outnumbered female victims in a ratio of about 4 to 1. In Scotland, Harris and colleagues[15] found a similar sex ratio, though the median age of their patients was about 40 years. Riggins and Kraus found that of 79 patients with cervical spine trauma admitted (not always initially) to a group of county hospitals in California, only 51% were male whereas 33% were women older than 65 years, but this was plainly a highly selected population.[16]

The proportion of patients injured in traffic accidents has varied considerably between series, doubtless reflecting differences in the life-styles of the populations studied. A larger percentage of patients was injured in traffic accidents in the Kentucky series[10] and particularly in our Arizona series than in those from southern California[4] or Maryland.[11] In the southern California series[4] the excess of traffic accidents was replaced by sports injuries and in that from Maryland[11] by falls (from high-rise buildings? Relatively fewer buildings in the Southwest than in the East are more than one story high). In a recent series from Edinburgh, Scotland—also a city of multistory buildings—20% of the injuries were due to falls and only 46% to traffic accidents.[15]

The proportion of patients who had been driving or riding in automobiles compared with those riding motorcycles and those who were pedestrians was fairly constant between series, but it can be shown that in ours, at least, the risk of neck injury to persons riding a motorcycle was six times greater than to those in a car. In Pima County, Arizona, where most of our patients were injured, motorcycles numbered only about 2.8% of all vehicles registered during the period of this study, while the mean number of occupants of all cars and trucks involved in accidents was 1.46 and for motorcycles it was 1.07 (Ms. Gail Brown, Accident Record Unit, Arizona Department of Transportation, oral communication, June 1986). Thus one might expect that motorcycle riders would account for about 2.05% of patients injured in traffic accidents. In fact, however, they comprised 11/86 (12%) of all persons injured in traffic-related accidents for whom adequate information is available, a significant excess ($P < .001$).

The continuing occurrence of severe neck injuries during water sports also gives cause for concern. Heiden and coworkers found that 23% of cases occurred in this way, including 17% sustained while diving,[4] and in the series of Soderstrom and associates, which also contained a large proportion (72%) of spinal cord injuries, 17% were diving accidents.[11] Although among our patients only seven were involved in diving accidents, three of them suffered permanent spinal cord damage. The necessity for continuing public education on the danger of diving into shallow water cannot be overstressed.

Situation of the admitting hospital. The experience that is

TABLE 3.—*Patient Populations, Causes and Patterns of Injury in 4 Recent US Series of Major Cervical Spine Injury**

Years of Survey	*California† 1963-1972*	*Maryland‡ 1976-1982*	*Kentucky§ 1979-1984*	*Arizona‖ 1980-1985*
Patients, No.	356	288	88	93¶
Mean age, yr	NS	35	28	30
Median age, yr	25	NS	25	25
Male patients, %	83	85	83	81
Vehicle injuries, %	50	53	72	79
Auto riders, %	43	50	65	68
Motorcyclists, %	5		5	9
Pedestrians, %	2	3	2	2
Falls, %	12	22	11	6
All sports, %	29	NS	9	10
Diving, %	17	17	NS	8
Other causes, %	9	7	8	5
Major associated injuries, %	NS	25	60	44
Spinal cord damage, %	(100)	72	36	29

NS = not stated

*Percentages are given as whole numbers.
†From Heiden et al.[4]
‡From Soderstrom et al.[11]
§From Reiss et al.[10]
‖This study.
¶Major injuries only

gained in a particular hospital of any sort of injury will be partly a function of its special purpose and facilities.[4,9,15] Another relevant factor is a hospital's geographic location. In Table 4 we have compared our series with that reported by Reiss and colleagues.[10] The data for both were collected during much the same period of time. They are almost identical in size, in the median ages of the patients and in the proportion of male victims in each series. The frequencies of the various causes of injury are also closely comparable. Yet there is a noticeable "shift to the right" of the spectrum of severity of injury in Reiss and co-workers' series compared with that of ours. The proportion of their patients suffering a neurologic deficit was significantly higher than ours, and more of their patients suffered a major associated injury ($.02 > P > .01$). Their patients suffered, on average, 2.3 major associated injuries each, whereas in ours the incidence was only 1.8, and nine of them died compared with only five of ours. Reiss and associates were plainly dealing with a more gravely injured series of people overall than we were. A likely explanation lies in the relative locations of their hospital and ours. Our hospital lies near the center of population of Tucson, but is not the closest hospital to the single freeway that traverses the city, and during the period covered by this report it had not been designated as a trauma center. By contrast, the hospital of Reiss and associates stands close to the intersection of two major crowded highways on which high-speed accidents are frequent (H.D. Garretson, MD, University of Louisville [Ky] School of Medicine, oral communication, June 1986). Severe intra-abdominal and intrathoracic injuries are known to occur more frequently in this type of accident than, for example, in sports injuries.[11]

TABLE 4.—*Percentage Frequencies (Whole Numbers) of Associated Lesions in Patients With Major Cervical Spine Trauma*

	Present Series (93 cases)	*Reiss et al, 1986[4] (88 cases)*
Neurologic deficits	34	45
Associated injuries		
Extraneural head	25	64
Intracranial	12	67
Spine (not cervical)	4	6
Thoracic	17	46
Abdominal	10	26
Extremities	23	23
Total with any associated injury		
1 or more major	44	60
Minor only	14	24
Deaths	5	9

Management

Soderstrom and colleagues found intra-abdominal injuries in 3 out of 58 patients who were in shock and had neurologic deficits following spinal cord trauma[11]; they emphasized that intra-abdominal and spinal cord lesions may occur together. They also reported three cases of "false-positive" peritoneal lavage, however. This fact, together with the two instances of negative laparotomy in our series, indicates that in interpreting an equivocal abdominal paracentesis in patients with upper cervical cord lesions, due weight must also be given to the fact that these often lead to gross arterial hypotension due to a loss of vasomotor control.

The efficacy of steroid therapy in the management of acute injuries of the spinal cord remains controversial.[17] In our series all such patients received some steroids, but the variety of drugs and dosages rendered the data unsuitable for statistical analysis. As already noted, there was no indication that one particular protocol was either more or less effective than the others. The most usual regimen was 100 mg methylprednisolone per 24 hours. None of the patients received amounts of steroid approaching 7 grams methylprednisolone or an equivalent in the first 24 hours, as some have urged.[18]

The proportion of our patients treated by an operation—40% of those with major cervical injuries—is very similar to that reported by Young and Dexter.[19] In both series the main reason for intervention was to stabilize a fracture or dislocation to allow earlier rehabilitation. Our finding that early surgical treatment has no effect on the ultimate degree of recovery of cord function agrees with the majority opinion.[15,19,20] Only one recent report claims a favorable effect for early surgical fixation of the cervical spine,[21] and in this paper, although a group of surgically treated patients subsequently attained higher motor test scores than a conservatively treated group, their scores on admission were also higher, and it can be calculated from the data that the improvement in scores was no greater for one group than for the other.[22] This finding and the considerable differences in the severity of both the cervical spine lesions themselves and their complications that appeared between two such outwardly similar series of cases as Reiss and associates[10] and our own underline the necessity for extreme caution in comparing the results of treatment of any but randomly selected series of patients.

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Oral Cholecystography and Sonography of Gallbladder in Cholecystectomy Patients

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In comparing the diagnostic specificity and sensitivity of oral cholecystography with that of sonography in 479 patients in a community hospital, the oral cholecystogram, when used with a double dose of contrast agent, showed greater specificity (1.00) and sensitivity (0.99) than the sonogram (0.54 and 0.94, respectively). Because of lower cost, the oral cholecystogram should be used as the initial diagnostic study when cholelithiasis is suspected, unless specific contraindications exist.

(Robles A, Devor D, Wang H, et al: Oral cholecystography and sonography of gallbladder in cholecystectomy patients. West J Med 1987 Oct; 147:432-434)

We compared the efficacy of double-dose cholecystography and sonography to determine specificity and sensitivity for diagnosing acute and chronic gallbladder disease in a community hospital. This study attempts to answer three questions: What are the specificity and sensitivity of oral cholecystography compared with those of sonography?, Is using cholecystography and sonography together better than relying on either technique alone? and What is the most reasonable diagnostic sequence to establish between cholecystography and sonography to determine gallbladder disease?

Methods

We reviewed the records of all patients who underwent cholecystectomies for any reason from July 1979 through June 1981. All 479 cases had complete records, including clinical histories, preoperative diagnostic studies, pathology studies and operative reports. The original radiographs and sonograms were available for review in all cases. The patients (355 women, 124 men) ranged in age from 10 to 85 years. The diagnostic equipment used was comparable to that generally available in modern community medical centers.

The patients underwent oral cholecystographies after receiving 6 grams of ipodate calcium (Oragrafin, E.R. Squibb & Sons, Inc, Princeton, NJ) the evening before. This is a double-dose technique and is routinely used for all adult patients. Multiple roentgenographic exposures were taken of the patients in at least two positions. Sonography of the gallbladder was done using B-mode digital gray scale scanners powered by 3.5-MHz transducers; static and real-time techniques were both used routinely. Transverse and longitudinal serial sector scans were made of the patients in at least two positions.

Radiologic examinations were classified as positive (diagnostic of gallstones or other abnormality), negative (diagnostic of normal gallbladder) or equivocal (nondiagnostic or uncertain interpretation). Results of sonographic examinations were classified as positive (gallstones present), negative (gallstones absent) or equivocal (gallbladder not visualized or study uninterpretable).

The 479 patients who had cholecystectomies were subject to various diagnostic studies based entirely on the preferences of the attending physicians and not because of any protocol requirement of a prospective study. The diagnostic studies included 367 cholecystograms, 241 sonograms, percutaneous transhepatic cholangiograms and nuclear scans. Computed tomography (CT) scans and intravenous cholangiograms were not used in this group. Two patients had cholecystectomies based on clinical findings alone.

Specificity was defined as the number of true-negative results divided by the number of true-negative plus false-positive results. Sensitivity was defined as the number of true-positive results divided by the number of true-positive plus false-negative results. Accuracy was defined as the number of true-positive plus true-negative results divided by the total number of cases studied.

Results

The diagnoses by the pathologist were chronic cholecystitis in 403 patients, acute cholecystitis in 67, cancer of the gallbladder in 3, normal gallbladder with cholelithiasis in 3 and normal gallbladder in 3. Acalculous cholecystitis was diagnosed in 14 of the chronic cases and in 4 of the acute cases. Women predominated in both acute (39 of 67) and chronic cases (312 of 403).

In 464 instances in which a diagnostic test preceded the cholecystectomies, multiple tests were carried out in 170 patients and single tests in 292 (Table 1). Transhepatic cholangiography was used in a few cases, but results from CT scans, endoscopic retrograde cholangiopancreaticograms and intravenous cholangiograms were never the bases of a diagnosis. In 160 patients, both oral cholecystographies and cholecystosonographies were done.

Cholecystectomies that were done without preoperative diagnostic studies—numbering 15—were not analyzed in this report. One patient explored for acute appendicitis was found

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to have acute cholecystitis, cholecystectomy was an incidental procedure in 12, and a clinical diagnosis alone was the basis for a surgical procedure in two patients (both diagnoses correct).

Oral cholecystographies were done on 367 patients, though in 25 instances they did not yield a diagnosis. "Faint visualization" was reported in 19 of these cases, and 6 others were noted to be "equivocally positive" for gallstones. Of these patients, 20 were subsequently found to have calculous cholecystitis and 3 had chronic acalculous cholecystitis; 2 were normal. Cholelithiasis was diagnosed in 215 cases; nonfunctioning gallbladder was diagnosed in 122. The five diagnoses of normal gallbladder included two diagnostic errors (one failure to detect stones and one failure to detect cholesterosis). There were no false-positive results. The specificity, sensitivity and accuracy were 1.00, 0.99 and 0.93, respectively.

Cholecystosonographies were done in 241 cases. Of these, 196 patients were diagnosed as having cholelithiasis or contracted gallbladder, 19 were diagnosed as having a normal gallbladder and 26 studies were uninterpretable. There were 6 false-positive reports (each suggesting cholelithiasis or a notably shrunken gallbladder) and 12 false-negative reports. The specificity, sensitivity and accuracy were 0.54, 0.94 and 0.82, respectively. In all, 160 patients had both oral cholecystographies and cholecystosonographies (Table 2). In 108 instances, the diagnoses obtained from both oral cholecystography and cholecystosonography agreed. In 52 cases, a discrepancy existed among preoperative studies. The oral cholecystography group included 25 correct interpretations, no false-positive reports and 4 false-negative reports. In all, 23 studies were judged to be nondiagnostic because of faint visualization or an equivocal finding of gallstones. Sonography provided a correct diagnosis in 18 instances, as well as 13 false-negative reports and 21 that were uninterpretable. Nine cases were not correct by either diagnostic method.

TABLE 1.—*Diagnostic Tests Preceding Cholecystectomy in 464 Patients*

Test	*Patients, No.*
Cholecystogram	367
Cholecystosonogram	241
Routine x-ray films (diagnostic)	6
Nuclear scans (PIPIDA)	18
Transhepatic cholangiogram	8

TABLE 2.—*Analysis of 52 Oral Cholecystograms and Ultrasonograms That Did Not Agree**

	Corrected	*False-Positive*	*False-Negative*	*Nondiagnostic*
Oral cholecystograms	25	0	4	23
Ultrasonograms	18	0	13	21

*108, agreement by both tests; 41, correct by one test, 9, not correct by either test.

Discussion

Single-dose oral cholecystography requires the administration of 3 grams of an absorbable oral contrast agent such as iopanoic acid (Telepaque, Winthrop Laboratories, New York), sodium tyropanoate (Bilopaque, Winthrop Laboratories) or ipodate calcium (Oragrafin). Large series[1] have shown that three fourths of patients so treated have satisfactory studies; two thirds of the remainder then have satisfactory studies if given an additional contrast agent, usually another 3 grams.[2] Administering additional contrast material fails to produce further improvement. The reported accuracy of double-dose studies varies from 0.92 to 0.95,[1,3,4] consistent with our results (0.93).

Comparison between studies is difficult because of case selection, population factors and methods of reporting data. Most studies are reported in terms of accuracy, but this mode is especially dependent on the incidence of an abnormality in the study group.[5] Similarly, there are differences in the preexamination preparation of patients, availability of facilities and radiologists' interest in doing certain studies.

There is a considerable amount of controversy in radiology literature about giving the most appropriate dose of contrast agent and following the correct sequence of studies.[6-8] Advocates of the single-dose technique generally administer an additional dose of contrast agent and recall a patient for further examination or refer the patient to a sonographer if the gallbladder is not visualized. The single-dose method can yield excellent results if there are careful preparation of the patient and dietary manipulation, but a nondiagnostic examination is still possible.

We believe the double-dose method is the most diagnostically effective and economically feasible method for a community hospital. The probability of achieving a definitive diagnosis at an initial examination is high. Patient anxiety from repeated examinations can be lessened, and there can be minimal inconvenience and loss of employment time. For a patient in hospital, a shorter stay is likely. The contrast agents used for the biliary system are safe, so that morbidity is negligible.[9] Contraindications to the use of oral cholecystography include sensitivity to iodinated compounds, pregnancy, gastrointestinal dysfunction and hepatic dysfunction.

Cholecystosonography has a reported accuracy of 0.78 to 0.99[3,10,11]; our results (0.82) were comparable. Combining sonographic and radiographic examinations improves the potential for diagnostic accuracy.

In our study sonography was a less reliable test than radiography but offered some special advantages. It is frequently applicable when a radiographic examination is contraindicated. It can also detect other abnormalities such as common duct or intrahepatic bile duct dilatation, common duct calculi and pancreatic cysts. The oral cholecystogram may also show stones, but in addition can demonstrate gallbladder function. Visualization of the gallbladder by oral cholecystography, however, depends on both gastrointestinal and hepatic activity as well as on gallbladder function. A nonvisualizing oral cholecystogram, therefore, does not necessarily reflect gallbladder function. Cholecystograms and cholecystosonograms do not provide precisely the same information and should be considered complementary rather than mutually exclusive or competitive procedures.

The high false-positive rate (low specificity) occurring with ultrasonography and the high number of "uninterpretable" readings reported in this study are of concern to us. This inability to interpret readings may be due in part to an ultrasonographer's level of interest or experience (or both) and the fact that most reports come from technicians interested in ultrasound and eager to show their proficiency in using it. Because a high degree of operator judgment and skill is required, ultrasound results are not always optimal. It is unreal-

istic to expect ultrasound results from a local hospital to be of the quality found in an academic teaching hospital; our failure to elicit results equal to those found in published reports may therefore reflect common limitations at most hospitals.

Economic considerations are germane in the choice of any tests. Oral cholecystograpy is the least costly study. At our institution, $67 is charged for an oral cholecystogram, $77 for a cholecystosonogram and $273 for a nucleotide scan.

The relative merits of any test must include cost as well as diagnostic efficacy. Now that the cost of medical care is being questioned by the government, the medical profession must order the most affordable and cost-effective procedures. We believe that our study helps in this quest. Our review also showed that our hospital generally prefers to use radiographic rather than sonographic diagnostic studies; each hospital should recommend preferred diagnostic studies after examining their own results, as opposed to uncritically accepting published statistics. The cost of reaching a diagnosis must also be evaluated before making any recommendation.

For suspected cholecystitis we recommend using oral cholecystography and cholecystosonography as follows:

- Use the double-dose oral cholecystogram as the initial study whenever possible.
- If the cholecystogram fails to show the gallbladder, probably because of a transiently altered physiology, repeat the cholecystogram when the patient's condition permits.
- If cholecystogram results are equivocal, do a sonogram.
- If a sonogram done initially was nondiagnostic or failed to show an abnormality and the contraindications to oral cholecystography no longer exist, do a cholecystogram.

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What to Do for Psoriasis

TOPICAL STEROIDS REMAIN THE MAINSTAY of therapy for most mild to moderate cases of psoriasis. Topical steroids in conjunction with coal tar preparations are probably the way the majority of my psoriasis patients are initiated into therapy.

The second preparation, anthralin, has gained popularity in the last two to three years. It is an age-old treatment that is very effective for psoriasis, but until about three to four years ago it was only available in a thick paste. It had to be compounded by a pharmacist and was very messy to use. In the last three to four years two companies have come out with a cream base anthralin, which makes it much more pleasant to use and makes it much more easily accessible. Anthralin, in combination with coal tar and topical steroids, is an extremely effective way to treat most patients with psoriasis.

Methotrexate is very effective for psoriasis but we reserve that for the severe or most resistant cases. Psoralen and ultraviolet A (PUVA) light is a very effective form of therapy, but, once again, it should be reserved for patients resistant to other modalities.

The retinoids represent something new and have been used only recently in the treatment of psoriasis, but they do show promise for the future.

—GORDON J. RUSSO, MD

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Medical Progress

Nutrition of the Fetus and Newborn

JAN M. KENNAUGH, MD, *and* WILLIAM W. HAY, Jr, MD, *Denver*

Both the successful development of healthy, long-term animal models to study fetal nutrition and metabolism and the improved survival of low-birth-weight, preterm infants have focused interest and research on fetal and neonatal nutrition and metabolism. Such a focus is important, given the recent emphasis on promoting neonatal growth in preterm infants at "normal" in utero growth rates. Estimates of nutrient requirements for growth in a human fetus remain ill defined, however. Body composition data appear biased toward thin infants. Animal data suggest that fetal nutrition proceeds according to species-specific growth rates, with variations in fat content largely dependent on placental fat permeability and on maternal nutrient supply as regulated by the placenta.

After birth, neonatal nutrition is affected primarily by food intake and the functional integrity and capacity of the gastrointestinal tract. Additionally, muscle activity, thermoregulation and stresses of various kinds and degrees modify a neonate's nutritional requirements. Functional deficits of the gastrointestinal tract have been circumvented by a more aggressive use of intravenous nutrition. Both intravenous and enteral nutrient mixtures have been substantially improved in the quantity of all nutrients and have been modified qualitatively toward compositions that are closer to those of human milk. These nutrient mixtures now produce plasma nutrient concentrations that approximate those of a healthy, breast-fed infant.

Although such efforts to improve the nutritional balance and growth of preterm infants have been successful, much remains to be learned about the nutritional requirements of sick infants.

(Kennaugh JM, Hay WW Jr: Nutrition of the fetus and newborn. West J Med 1987 Oct; 147:435-448)

In the past 15 to 20 years, considerable clinical and scientific interest has focused on the nutrition of human fetuses and newborn infants, particularly preterm infants. Much of this interest has been the result of two factors. The first is the remarkable success of saving the lives of preterm infants of very low birth weight who then need to be nourished for "normal" growth and function. The second is the development of unstressed fetal animal models that have allowed the nutrition, metabolism and growth of a fetus to be measured directly *in vivo*.

Standards for nutrition of full-term infants have been based, with reasonable logic and accuracy, on the nutrient intake and growth of healthy, breast-fed infants. In contrast, a major problem with the nutrition of preterm infants of low birth weight has been to define what "normal" nutrition should be. For example, although the American Academy of Pediatrics has chosen the normal intrauterine growth rate as the primary goal for nutrition of preterm infants, even a casual observer can see (or imagine) how grossly different the two conditions—normal fetus and preterm infant—are. Such differences include, for example, the environment (warm amniotic fluid versus conventional heated incubator or overhead radiant warmer), the dietary supply (continuous umbilical blood flow supplying nutrients from the placenta versus intermittently given milk or formula through the immature gut or nutrient mixtures given intravenously through a peripheral vein) and the physiologic condition of an infant (relatively stress free and dependent on placental and maternal control versus the stresses and illnesses of a preterm infant characterized by the many clinical problems of these infants and their treatments in a newborn intensive care unit). Thus, even if human fetal nutritional and growth data were available—or data extrapolated from animal models that closely resemble a human fetus—exclusive use of such data for directing postnatal human nutrition would provide at best only rough estimates for recommended nutrient intakes of preterm infants. Nutrient requirements for preterm infants have been based also on estimates of changes in intrauterine chemical composition. Widdowson and Dickerson collected data from the compositional analysis of stillborn preterm infants, allowing construction of a reference human fetus.[1] Calculations of the appropriate nutrient intake and growth based on this reference fetus are reasonable goals, with certain limitations. As Sparks has pointed out, the study population was probably skewed towards "abnormal," with a preponderance of thin, small-for-gestational-aged infants.[2] Additionally, body composition data give information only about net tissue accretion and thus reflect only minimal nutritional requirements. Neverthe-

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less, with these limitations, intrauterine growth has been accepted as a reasonable goal for postnatal nutrition of preterm infants.[3]

Fetal Nutrition

Role of the Placenta

The nutrient supply to a fetus is dependent on placental transport. Data collected by Molteni and co-workers show that in humans the placenta grows rapidly in size during early gestation, with a slightly slower growth after 32 weeks' gestation until term (Figure 1).[4] In contrast, the functional capacity of a placenta to transport nutrients increases significantly during late gestation.[5] For example, morphometric studies in human placentas have shown that the placental thickness decreases and the surface area continues to increase exponentially until term.[6] Additionally, studies in sheep placentas have shown an increasing placental diffusion and transport capacity for substances such as urea[5] and glucose (R. Molina, MD, W. W. Hay, Jr, MD, and G. Meschia, MD, unpublished data, 1986-1987). Similarly, there is an increase in absolute blood flow to the uterine and umbilical circulations with advancing gestation. These observations imply that the growth and maturation of a placenta are geared to the growth of fetal nutrient requirements. Less is known about developmental changes in placental transport of individual nutrients, although indirect evidence for glucose and fatty acids suggests increasing placental transport capacity towards term, and certainly the bulk of protein transfer occurs after 30 weeks of gestation when a fetus triples in size, while the placenta increases by only about 50% in weight. Thus, despite a tendency for placental weight to plateau in late gestation, the functional capacity continues to increase, suggesting the means by which an adequate nutrient supply is maintained at term under normal conditions.[7] As shown in Figure 1, however, the size of a fetus is directly related to the size of the placenta over the last half of gestation. Thus, both the placental size and placental nutrient transport capacity combine to help determine fetal growth.

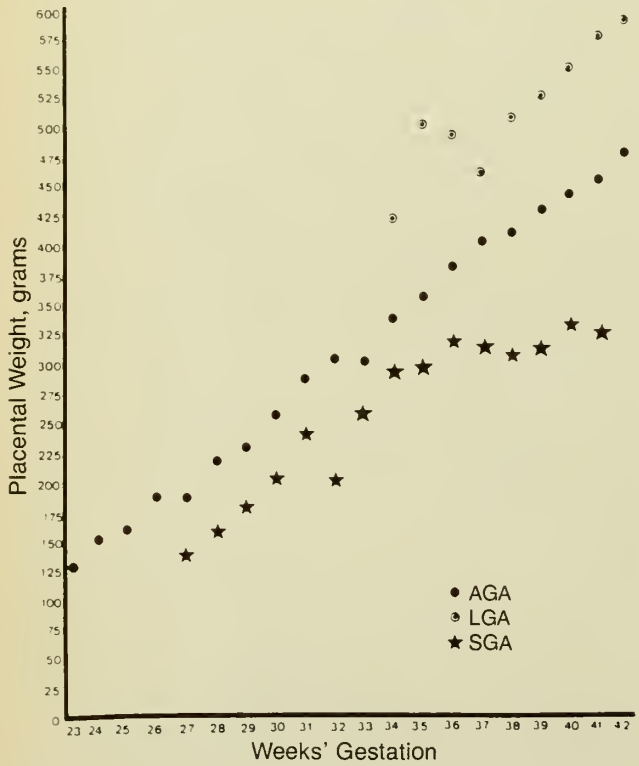

Figure 1.—Mean placental weight for human infants who are average for gestational age (AGA), large for gestational age (LGA) and small for gestational age (SGA) from 23 to 42 weeks of gestation. From Molteni et al,[4] reproduced with permission of the *Journal of Reproductive Medicine*.

The placental transport of nutrients to the umbilical circulation depends on the permeability of the placenta to each nutrient, the maternal-to-fetal concentration gradient for each nutrient, net placental nutrient consumption and the magnitude and pattern of uterine, placental and umbilical blood flows. The placenta is not equally permeable to all compounds, and different mechanisms for transport exist for various groups of nutrients. For example, placental transport of water and gases occurs by simple diffusion and is sufficiently rapid for these substances that the transport capacity is limited by the blood flow. Hence, such substances are considered "flow-limited" with respect to placental transport. In contrast, glucose and lactate transport is carrier-mediated, and amino acid transport is active or energy dependent. For these substances, transport is limited by the rate of diffusion. Thus, their placental transport is considered "diffusion-limited."

The maternal-to-fetal nutrient concentration gradients are subject to changes in maternal arterial nutrient levels that are altered by diet, fast-feed cycles and hormonal influences. The relationship between the maternal arterial concentration and the placental transport of nutrients appears to be direct (positive) but nonlinear.[7] Such a relationship also holds for uterine or umbilical blood flow and the placental transport. Examples from experiments in sheep of the effect of changes in uterine and umbilical blood flow on the fetal uptake of oxygen are shown in Figure 2.[8]

The placenta is more than a passive conduit for nutrient supply to the fetus. It is also a metabolically active organ, consuming oxygen, glucose and amino acids and producing substances such as lactate that are important for fetal metabolism and growth. In sheep, about 50% of the oxygen and 65% of the glucose supplied by the maternal circulation to the uteroplacenta are consumed by these tissues. Some nutrients important in fetal metabolism (lactate, ammonia) are not

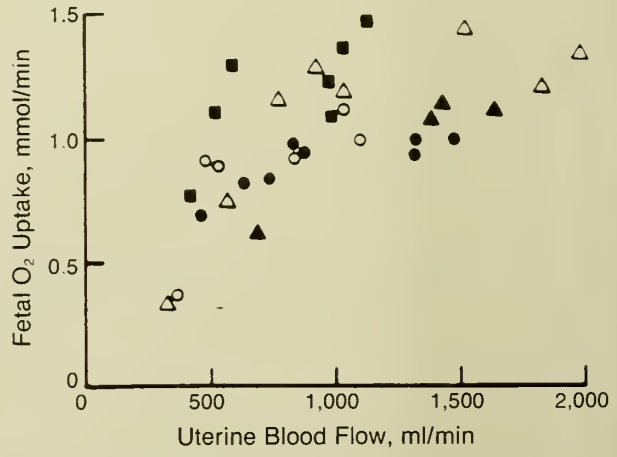

Figure 2.—The relationship between fetal oxygen uptake and uterine blood flow in term fetal lambs, showing that at normal uterine blood flow rates—greater than 1,000 ml per minute—fetal O_2 uptake does not change with uterine blood flow; at uterine blood flow rates of less than 1,000 ml per minute, fetal O_2 uptake falls progressively with a further decrease in uterine flow. The symbols represent individual animals studied. From Wilkening and Meschia,[8] reproduced with permission of the American Physiological Society.

transferred from the maternal circulation to the fetus but are actively produced in the placenta.[9] Figure 3 is a summary of what is known from in vivo studies of the metabolism and transport of nutrients by sheep placenta, as an example of the complex role played by the placenta in fetal nutrition.[10] In vitro data for the human placenta, obtained from a variety of models—perfused whole placenta, perfused lobule, tissue slice incubation and cell culture—suggest qualitatively similar metabolic and transport processes for the human placenta.

Requirements for Fetal Growth and Metabolic Rate

Fetal nutrient requirements are determined by the rate of growth, the composition of new tissue and the metabolic rate.[11] The process of growth is complex because there is ongoing turnover and remodeling of tissue in addition to net accretion. Data extrapolated from studies of animals regarding growth must be accepted with great caution because growth rates vary considerably among species. For example, a human fetus grows an average of 1.5% per day from midgestation to term, lambs at 3.5% per day and rats at 30% per day. The composition of new tissue also varies among animals, principally in its fat content. Compared with the ovine species, a human fetus deposits larger amounts of fat, which has a greater caloric value (9.5 kcal per gram) than nonfat tissue (Figure 4). Thus, despite a slower growth rate, a human fetus has a higher caloric accretion rate (40 kcal per kg per day) than does a lamb (30 kcal per kg per day).[12]

The fetal metabolic rate has been determined primarily by measuring the rate of fetal oxygen consumption and multiplying this rate by the average oxidative caloric equivalent of the fetal fuel mix (assumed to be primarily glucose and amino acids with 4.5 kcal per gram). Data from a number of species suggest that the weight-specific rate of fetal oxygen consumption is relatively constant among species. The reason for this interesting phenomenon is not clear but may represent the means by which a relatively small animal may produce a relatively large offspring, which may provide survival value for the offspring without adding an inordinate stress to the pregnant mother. An estimate of human fetal energy requirements is presented in Table 1.[12]

Individual Nutrients

Carbohydrate

Placental glucose transport occurs by facilitated diffusion, shown by the observation that the rate of umbilical glucose uptake—the net placental-to-fetal glucose transport—is directly related to both maternal plasma glucose concentration and the transplacental glucose concentration gradient up to a maximum rate of uptake.[15] Glucose uptake by human fetuses has not been measured. In fetal lambs the glucose uptake rate under normal conditions is about 4 mg per kg per minute, which is similar to the use rate of glucose by preterm and term human infants as measured by isotope dilution techniques.[16,17]

In fetal lambs, glucose use is directly dependent on the glucose concentration of both mother and fetus and on the fetal insulin concentration.[18] For example, during maternal fasting-induced hypoglycemia there is a fall in umbilical glucose uptake and glucose use, while glucose infusion-produced hyperglycemia and a higher fetal insulin concentration (at any glucose concentration) increases fetal tissue glucose use.[18] These results provide a picture of fetal glucose metabolism remarkably similar to that derived from human studies that show that whole-body glucose metabolism tends to follow saturable, carrier-mediated kinetics. Studies in pregnant sheep and fetal lambs have shown that insulin, either maternal or fetal, does not directly regulate placental glucose transport; rather, insulin leads to an increase of umbilical glucose uptake by enhancing fetal glucose use, producing fetal hypoglycemia and an increased fetal-to-maternal glucose concentration gradient.

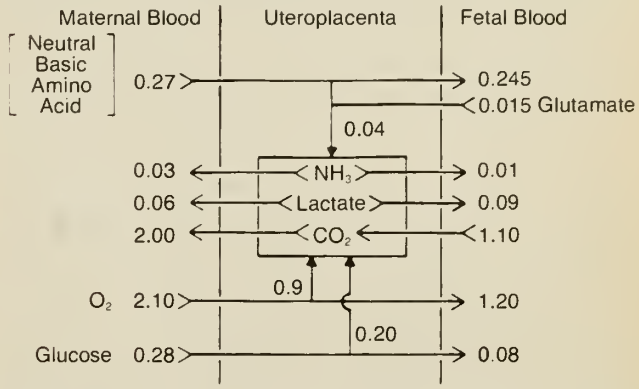

Figure 3.—A summary of the net substrate fluxes in and through an ovine uteroplacenta in the last two weeks of gestation. The fetal weight is assumed to be 4.0 kg. Amino acid fluxes are given in nitrogen mEq per minute and all other fluxes in mmol per minute. From Meschia et al,[10] with permission of *Federation Proceedings*.

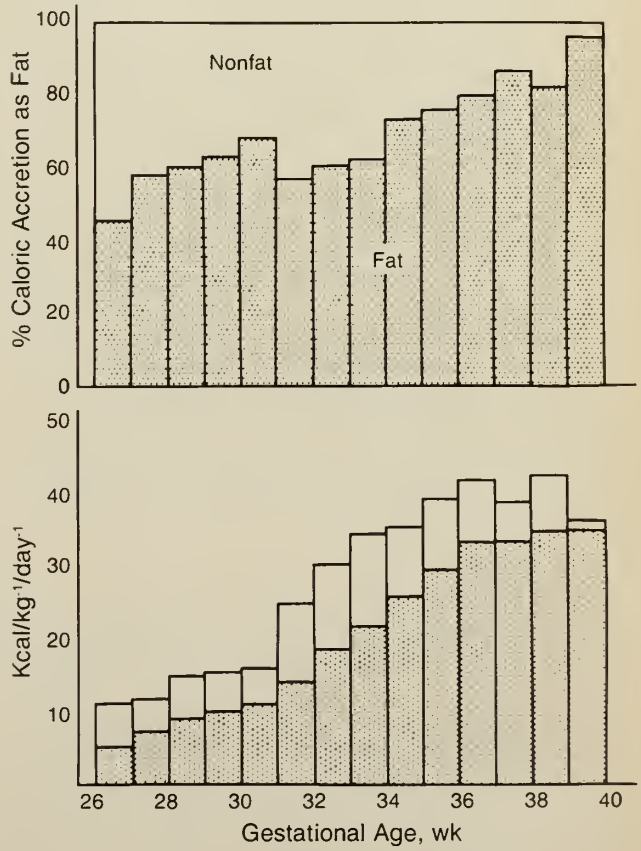

Figure 4.—Estimated caloric accretion in a human fetus during the last 14 weeks of gestation. Upper graph: Fat and nonfat accretion are presented as the percent of total caloric accretion. Lower graph: Daily caloric accretion for fat (stippled portion of bar) and nonfat (total height of bar) tissue. Reproduced from Sparks et al,[12] with permission of S. Karger AG, Basel.

TABLE 1.—*Estimates of Human Energy Requirements**†

Energy Requirement	*Term Fetus*	*Preterm Infant*	*Term Infant*
Basal metabolism	50	47	48
Growth	43 (10 for nonfat dry weight, 33 for fat)	80	33
Activity, losses (stool)	—	22	45
Total	93	149	126

*Kcal/kg/day
†From Sparks et al.[12] Reichman et al[13] and Widdowson[14]

Theoretically, the fetal glucose pool may have both exogenous and endogenous sources. The placenta provides glucose exogenously from the maternal circulation whereas the fetus may produce glucose from a glycogen breakdown or synthesis from other carbon sources. In fetal lambs during normoglycemic conditions, the rates of umbilical glucose uptake and fetal glucose use are the same, suggesting no fetal endogenous glucogenesis under such conditions. During fasting-induced hypoglycemia, however, fetal glucose use exceeds umbilical glucose uptake (at glucose uptake rates of less than 50% of normal), suggesting that fetal glucogenesis in this species in late gestation may contribute to fetal glucose homeostasis.[19]

Glucose is an important but not sole metabolic fuel for a fetus. In fetal lambs, brain, heart and skeletal muscle are glucose-dependent tissues, but, overall, only about 50% of the oxygen consumption can be accounted for by complete glucose oxidation.[7] The human fetus may be even more dependent on glucose for oxidative metabolism given the large brain-to-body weight ratio in newborn humans—three to four times that of any other species[20]—and the estimate that nearly all of the glucose consumed by human infants is consumed by the brain.

Lactate, while usually associated with hypoxemia and ischemia, is an important fetal nutrient under normoxemic conditions. It is produced in the placenta (and in the fetus) and consumed in net by the fetus, contributing significantly to fetal carbon and energy sources. Specifically, lactate (and acetate) appears to be a major contributor to fetal fat synthesis in the fetal calf,[21] and lactate provides as much as 25% of oxidative metabolism in the fetal lamb.[22] The human placenta also produces lactate, and data from umbilical cord blood sampling at a cesarean section from "unstressed" human infants suggest that lactate may be an important nutrient for the human fetus as well.[23]

Protein and Amino Acids

The concentration of amino acids in fetal plasma is higher than that in maternal plasma. Thus, the placental transfer of amino acids to a fetus occurs against a concentration gradient by active transport mechanisms. Unfortunately, the regulation of such active transport mechanisms has received little direct investigation, particularly with respect to what extent placental amino acid transport is affected by maternal or fetal amino acid levels, oxygen supply or the supply of energy substrates or cofactors.

In fetal lambs—the only species in which the umbilical uptake of amino acids has been measured—the net umbilical amino acid uptake exceeds the requirements for the net fetal protein accretion,[24,25] delivering about 1.6 grams nitrogen per kg per day (160% of nitrogen requirements) as 6.9 grams protein per kg per day (Figure 5). It is also the primary source of carbon (5.3 grams carbon per kg per day, or 60% to 70% of fetal carbon requirements in fetal lambs), exceeding the uptake of glucose and lactate carbon combined. The acidic amino acids do not appear to be taken up in excess of accretion. Thus, the fetal synthesis of these amino acids may be necessary for a fetus to ensure adequate protein for growth. The estimates of ovine amino acid uptake probably exceed those of a human fetus because the ovine fetal growth rate is greater than that in a human and is accompanied by minimal fat accumulation.

In addition to the incorporation of amino acids into protein accretion, a high fetal urea production rate, found in both sheep and primates, suggests a role for amino acids as metabolic fuel.[26] Studies in fetal lambs using leucine labeled with carbon 14 support this hypothesis, documenting a high rate (25% of disposal) of leucine oxidation measured as irreversible carbon dioxide 14 production.[27] With maternal fasting and a decreased umbilical glucose supply, the fetus diverts amino acids from protein synthesis to use as metabolic fuel. For example, fasting of pregnant sheep was shown to double the ratio of the fetal leucine oxidation rate to the leucine disposal rate (Figure 6).[28] Fetal oxidation has been observed also for alanine, glycine, lysine and tyrosine. Amino acids thus may be important in supplying energy for basal metabolism and as alternate fuels during energy deficiency.

Amino acid tracers also can be used to measure the fetal protein synthetic rate. Experiments of this nature have been done in fetal lambs using lysine ^{14}C and leucine ^{14}C. Results of these experiments in fetal lambs have shown that the fractional protein synthetic rate in late gestation is twofold to threefold greater than the fractional rate of growth, further supporting the concept that fetal protein turnover is high and capable of providing carbon for energy production as well as for growth.

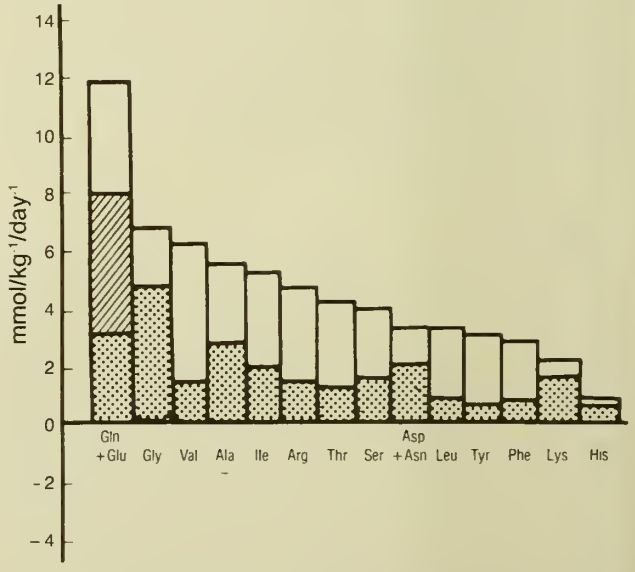

Figure 5.—Comparison of daily net fetal umbilical uptakes of individual amino acids (entire bar) with corresponding daily rates of whole-body net accretion of amino acids (stippled portion of bar) in fetal lambs. The hatched portion of the Gln + Glu bar represents umbilical glutamate excretion. From Meier et al,[25] reproduced with permission from the Society for Experimental Biology and Medicine. Ala = alanine, Arg = arginine, Asn = asparagine, Asp = aspartic acid, Gln = glutamine, Glu = glutamic acid, Gly = glycine, His = histidine, Ile = isoleucine, Leu = leucine, Lys = lysine, Phe = phenylalanine, Ser = serine, Thr = threonine, Tyr = tyrosine, Val = valine

The concentration of amino acids also may be important in regulating the level of fetal insulin, the primary fetal "growth hormone." For example, studies in human neonates by Grasso and associates have shown pronounced enhancement of insulin secretion by intravenous infusion of amino acids plus glucose when compared with infusing only glucose.[29] Insulin excess in a fetus may increase fetal amino acid uptake from the placenta, increase amino acid entry into net protein accretion—perhaps by substituting glucose for amino acid oxidation—or both. Not all species show an increased fetal growth response to increased levels of fetal insulin. This response has not been observed in fetal lambs, although insulin deficiency in a fetal lamb, produced by fetal pancreatectomy, appears to reduce the fetal growth rate.

Fat

Much less is known about fetal fat nutrition and metabolism than for glucose and amino acids. First, only a few species—human, guinea pig, rabbit—have placentas permeable to fat or that lay down fat in the fetus to any appreciable degree (human, 18% of body weight at birth; guinea pig, 10%; rabbit, 7%).[1] Because increased concentrations of maternal lipids do not generally occur in maternal plasma in pregnancy except during fasting, placental permeability to lipids appears to be the major factor regulating fetal lipid uptake. The placenta conceivably can transport fat to the fetus by specific fatty acid carrier-mediated diffusion, by synthesis de novo and by hydrolysis of triglycerides, lipoproteins and phospholipids that are taken up by the placenta as macromolecules. Even less is known about the fate of such lipids taken up by a fetus. Relatively low levels of plasma and tissue carnitine in fetuses make it appear unlikely that fats contribute much to fetal energy balance although, in humans at least, an immediate postnatal fall in the respiratory quotient suggests a quite rapid switch to fatty acid oxidation before milk is provided with enough carnitine to increase the functional component of this key factor in lipid metabolism.

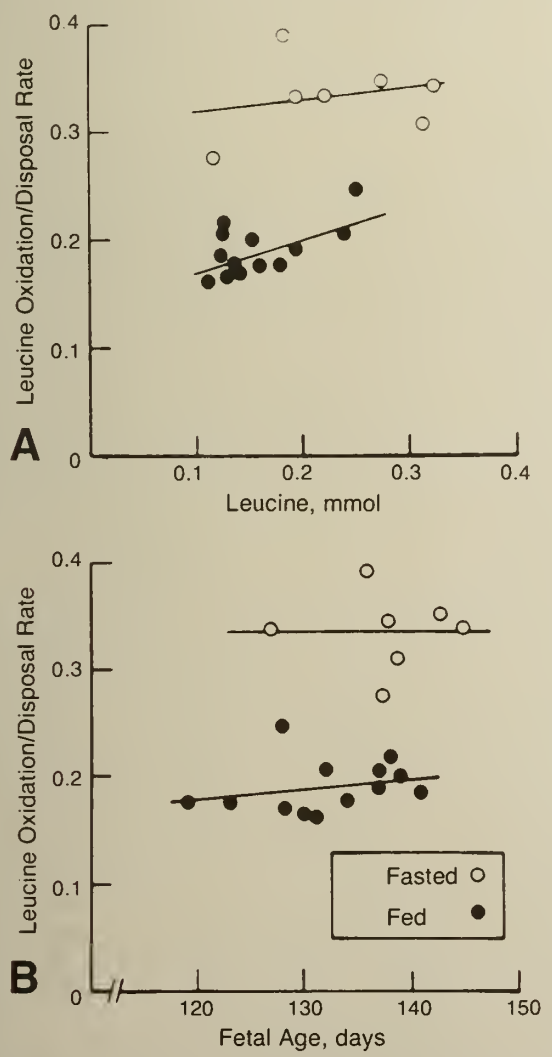

Figure 6.—Plot of fetal leucine oxidation/disposal rate ratio versus fetal arterial plasma leucine concentration **(A)** and fetal age **(B)**. Observations in fed ewes are compared with observations in ewes in the fourth to eighth day of fasting. From van Veen et al,[28] reproduced with permission from *Metabolism*.

Summary

Estimates of nutrient requirements for growth in a human fetus remain ill defined. Body composition data appear biased toward thin infants. Additionally, turnover measurements for human fetal nutrients have not been done and thus actual nutrient intakes cannot be calculated or compared with net accretion rates. Nevertheless, animal data suggest that fetal nutrition proceeds according to species-specific growth rates, with a variation in fat content largely determined by placental fat permeability. Also, the fetus is solely dependent on the mother for nutrient supply but, through placental and fetal mechanisms, fetal metabolism and growth can proceed with some autonomous regulation in response to maternal nutrient insufficiency.

Neonatal Nutrition

Fetal nutrient delivery changes at birth from a continuous intravenous supply from the placenta to intermittent gastrointestinal feedings. The form and composition of the diet are also altered with the introduction of milk. Despite this transition, growth continues to be rapid, though increasingly slower than the rapid fetal growth rate. Weight increases threefold to fourfold during the first year, with the fastest growth rate in the first few months.[30,31] Healthy infants usually gain between 25 and 40 grams per day during the first three months and 15 to 20 grams per day during the fourth through the sixth months of age (Figure 7).

In contrast to the decreasing growth rate, the metabolic rate increases immediately after birth, largely due to muscle activity and thermal regulation. An estimate of the total energy needs for term infants in the first six months is about 115 kcal per kg per day, which falls gradually to about 105 kcal per kg per day by the end of the first year. Preterm infants may require 120 to 150 kcal per kg per day to achieve the in utero growth rate.[32–35] The energy requirements for human fetuses, preterm infants and term infants are compared in Table 1.[13,14]

Nitrogen and Energy Balance

Two methods have been used to assess protein requirements in newborn infants. The first has been to use the protein intake and the growth rate of infants fed by their own mother's milk on an ad libitum, demand basis. This method is problematic because the protein content of milk varies over time and milk intake has been difficult to quantify accurately. By this method, growth rates and protein intakes are lower in preterm and term infants when compared with similar infants fed with formula on ad libitum, demand schedules. The second method

involves the calculation of protein requirements based on growth and maintenance of "normal" infants. Only estimates of such requirements have been made for postnatal infants, based on nitrogen balance and protein turnover studies. For preterm infants, references to nitrogen and protein growth have been based also on body composition data from infants who have died. Not available for human fetuses and infants, however, is important information about the extra amount of protein intake used for metabolic purposes other than net protein accretion, which, as shown in Figure 5 for fetal lambs, may be considerable.

Additional modification of protein requirement comes from the change in nonprotein caloric intake. Following birth, fat intake from milk or formula increases substantially. Whether or not the nonprotein caloric intake is greater in infants than in fetuses, for humans at least, is not known. Considerable attention has been paid recently, however, to quantifying the separate and combined effects of protein and nonprotein energy intake on nitrogen balance and growth. Several studies have clearly documented that increasing energy intake when nitrogen is excluded from the diet results in a reduction of nitrogen excretion and a more positive nitrogen balance. When nitrogen intake is increased at "adequate" (roughly "normal") energy intake, nitrogen retention and nitrogen balance also increase. Together, increasing energy and nitrogen intakes promote nitrogen retention and balance,

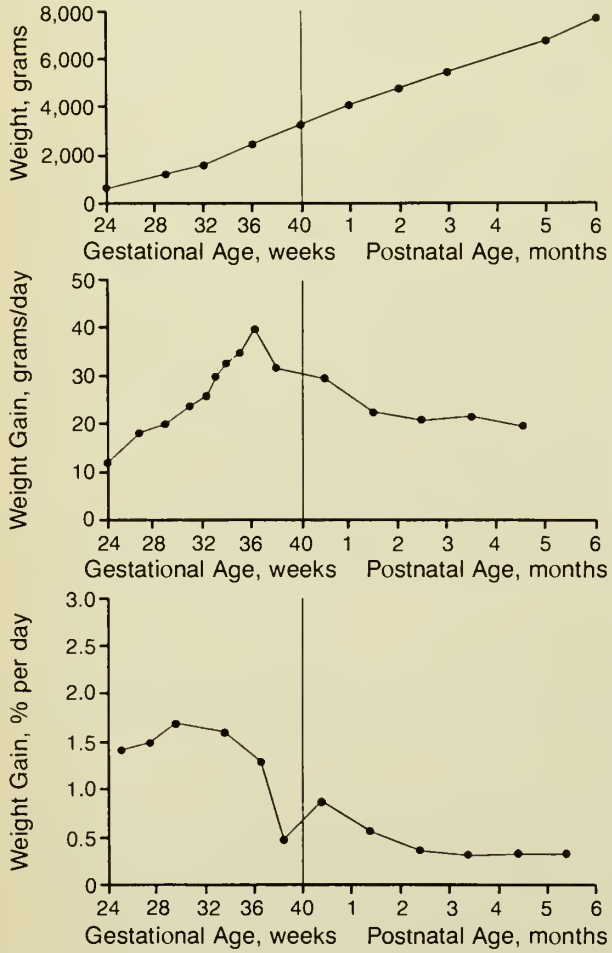

Figure 7.—Human fetal and neonatal weight gain is approximately linear from 24 weeks' gestation through the first 6 months of life, but the weight-specific calorie and nitrogen requirements for this rate of growth peak during fetal life when the rate of weight increase per day is maximum. Adapted from Widdowson and Dickerson.[1]

although a maximum nitrogen balance is reached at each level of nitrogen intake when the energy intake exceeds 70 kcal per kg per day. At this energy intake, the nitrogen balance does not appear to increase when the nitrogen intake exceeds about 650 mg per kg per day (about 4.0 grams per kg per day protein). At lower energy intakes (< 70 kcal per kg per day), nitrogen intakes of greater than about 500 mg per kg per day do not provide a greater nitrogen balance. In either case, "excess" protein may lead not to nitrogen retention but to increasing urinary protein excretion and elevated plasma urea and amino acid concentrations,[36] and "excess" energy intake may promote fat deposition and an increased metabolic rate, the latter occurring potentially at the expense of growth.

These data and conclusions about energy and nitrogen balance are derived from relatively normal preterm infants. Considerable variation exists, particularly among infants with different disease states. For example, sophisticated energy balance studies have shown that infants with bronchopulmonary dysplasia have a much increased resting metabolic rate and that considerably higher amounts of nonprotein calories are needed to maintain normal growth.[37] Also, studies of infants with necrotizing enterocolitis who also have an operation have suggested that the metabolic rate may be increased in some of these infants and, in many, increased protein requirements are the result of a protein-losing enteropathy and excess urinary nitrogen loss.[38]

Carbohydrate

A newborn's diet consists of lactose as the primary carbohydrate. It is a disaccharide composed of glucose and galactose, providing about 40% of calories in infants fed mature human milk or a standard "humanized" formula. Lactose is cleaved into glucose and galactose by lactase that is present in the brush border of the small intestine by 24 weeks' gestation, increasing rapidly from 32 to 38 weeks. At term, lactase levels are two to four times higher than those of babies 2 to 11 months of age. Breath hydrogen studies confirm the functional capacity of neonates to digest and absorb lactose. Glucose and galactose are actively transported into portal venous blood in the jejunum and ileum by a specific adenosine triphosphate-dependent protein carrier that cotransports sodium.[39-41]

Although earlier studies suggested that preterm infants may have inadequate lactase activity to handle the normal dietary supply of lactose, resulting in modest carbohydrate malabsorption and osmotic diarrhea, such problems are seldom clinically significant. Lactose intolerance also has been recorded in severely ill infants with diarrhea, which has resolved with the substitution of formulas containing other carbohydrates (sucrose, Polycose [Ross Laboratories, Columbus, Ohio]). A recent study suggests, however, that infants with mild gastroenteritis recover regardless of which carbohydrate is ingested, suggesting a clinically negligible contribution of lactose malabsorption to the diarrhea in this situation.[42] Also, glycosidase enzymes are present in the small intestine that allow more complete digestion of glucose polymers (for example, corn syrup solids, dextromaltose, Polycose).[43] As a result, formula manufacturers have changed their premature infant formulas to contain 40% to 50% lactose and 50% to 60% glucose polymers. Because the glucose polymers are large, they provide an additional advantage of decreasing the initial osmotic load of a feeding. Other studies have emphasized the importance of lactose in the diet of

preterm infants. Galactose derived from lactose hydrolysis is cleared from portal blood by the liver where it contributes to glycogen formation and thus the important potential for glucogenesis between feedings. Also, lactose itself appears to be an essential ingredient of milk that enhances lactase and maltase enzyme activity leading to improved disaccharide digestion.[44]

Other disaccharidases (sucrase, maltase, isomaltase) in the small bowel reach mature levels by 28 weeks' gestation. Salivary amylase is present at birth, and the pancreatic amylase concentration is low at birth (10% of adult value) and throughout the first year of life[39-41]; their contribution to carbohydrate digestion in preterm infants is unknown.

After birth, neonatal plasma glucose concentration decreases initially, rising to greater than 60 mg per dl after 8 to 12 hours. Because of the brain's dependence on glucose, most physicians today strive to keep an infant's plasma glucose concentration greater than 50 to 60 mg per dl (comparable to the fetal level), providing early feedings or intravenous glucose if the plasma glucose value is below this level. Earlier studies documented much lower average postnatal glucose levels—20 to 30 mg per dl and 30 to 40 mg per dl in preterm and term infants, respectively—although such infants were fasted relative to infants today.

The newborn's central nervous system is similar to that of the fetus in its dependence on glucose as an energy source. About 4 mg per kg per minute of glucose is provided by a normal intake of breast milk (150 ml per kg per day) in a term infant, a rate comparable to the estimated glucose use rate by the brain.[14] Thus, lack of an appropriate glucose supply can be quickly deleterious to brain tissues. Liver glycogen stores increase during gestation, but the capacity for endogenous glucose production by glycogenolysis or gluconeogenesis may not be fully developed in newborns, especially in preterm infants.[11]

Glucose infusion. Infusing glucose intravenously into healthy preterm infants produces plasma insulin and glucose concentrations and whole-body glucose use rates directly related to the rate of glucose infusion (Figure 8).[45] Precisely where the glucose goes—protein accretion, fat, glycogen stores and the like—is not known, but infants fed intravenously over long periods by high glucose infusion rates (> 10 mg per kg per minute) frequently appear obese and fatty livers may develop. Also, data from fetal lambs show an inverse relationship between fetal glucose use and leucine oxidation[28] and a direct relationship between fetal glucose use and glucose oxidation,[46] both observations suggesting that glucose in excess of basal metabolic needs can substitute for the oxidation of other substrates. Perhaps in this way, excess glucose can lead to fat deposition and a more positive nitrogen balance.

Regardless of the exact rate of glucose required for normal brain and tissue use, most physicians provide glucose at about 5 to 6 mg per kg body weight per minute to avoid hypoglycemia. Glucose infusion rates of this magnitude usually result in normal to slightly high plasma glucose concentrations (80 to 120 mg per dl) within 30 to 60 minutes. At this rate, glucose provides about 30 to 35 kcal per kg per day or about two thirds of the calories required to maintain basal oxidative metabolism and prevent excessive nitrogen loss. Over several days, glucose infusion rates can be increased slowly to about 10 mg per kg per minute (for example, 12.5 mol per liter dextrose solution at about 5 ml per kg per hour) or about 58 kcal per kg per day, which is close to the caloric requirement to prevent substantial protein catabolism and reduce nitrogen loss to near zero.

Excess intravenous infusion of glucose (> 10 mg per kg per minute) has led also to a greater degree of hyperglycemia (along with glycosuria), particularly in very small preterm infants.[47] Such infants are presumably under considerable stress and produce increased levels of insulin-counterregulatory hormones—cortisol, glucagon, adrenalin—that may interfere with glucose use and exaggerate endogenous glucose production (directly and by inhibiting insulin suppression of glucose production). Two observations support the concept of stress-mediated inhibition of insulin action and increased glucose production. First, this condition of hyperglycemia in such infants disappears over several days as the infants' conditions improve. Second, in normal rat pups, insulin-stimulated glucose uptake by diaphragm muscle increases with advancing postnatal age.[48]

Protein and Amino Acids

The appropriate protein intake for newborn infants is not as well understood as their carbohydrate needs. Estimates for healthy term babies range from 1.5 to 4 grams per kg per day. The body protein content increases from 11% to 14.6% during the first year, averaging an absolute gain of 3.5 grams per day from 0 to 4 months of age. Infants show a greater net protein accretion than older children, using about 60% to 70% for growth versus 10% to 15% in the toddler age group. The minimum protein intake for term infants over the first few months of life suggested by the Food and Drug Administration is 1.8 grams protein per 100 kcal of body metabolic rate.

There are nine essential amino acids for humans—isoleucine, leucine, threonine, lysine, methionine, tryptophan, valine, histidine and phenylalanine. Preterm infants may also require provision of three additional amino acids—tyrosine, taurine and cysteine—suggested by low levels of enzymes necessary to produce these amino acids from precursors and by the dependence on dietary intake to maintain normal plasma concentrations of these amino acids.[49] They are also relatively increased in concentration in breast milk.

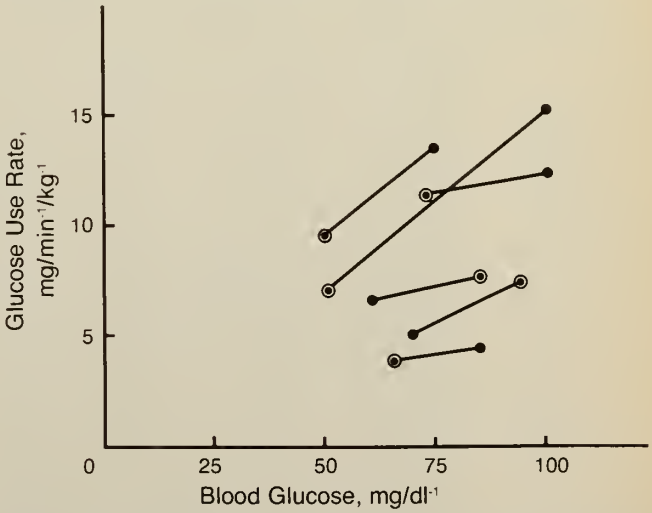

Figure 8.—The glucose use rate, measured with a [6,6-*d,d*]-glucose tracer in preterm human infants, is shown to increase for an increase in glucose concentration or to decrease for a decrease in glucose concentration (• = first and • = second glucose concentration) during intravenous glucose infusion. 0.058 standard deviation mg/kg/min per change of 1.0 mg/dl of blood glucose concentration. From Zarlengo et al,[45] reproduced with permission of *Biology of the Neonate*.

Protein digestion and absorption of amino acid and peptides in the newborn are not well studied. Gastric pepsin activity is low, but increases rapidly after birth. Trypsin and chymotrypsin are produced by the pancreas, and their activity also increases in the postnatal period.[39]

Human and bovine milk differ in protein and amino acid composition. Breast milk has less total protein than cow's milk. It contains about 1% protein, compared with 3% in cow's milk and 1.5% in commercial formulas. The amino acid composition also differs because of characteristic amino acid profiles of casein and whey proteins. Caseins are the predominant proteins in bovine milk—80%, compared with only 30% of total proteins in human breast milk. The predominant proteins in breast milk are whey, accounting for about 65% of proteins versus 21% in cow's milk.[49]

The predominant whey protein in cow's milk is lactoglobulin, which is not present in human milk and has been implicated as the major allergenic protein of cow's milk. The five major whey proteins in human milk are lactalbumin, serum albumin, lactoferrin, lysozyme and immunoglobin (primarily secretory immunoglobulin A).[49] The last three proteins are not digested and absorbed in the gastrointestinal tract and thus are not nutritionally available to an infant. Raiha has calculated the protein intake of a healthy term breast-fed infant to be about 1.5 grams per kg per day. In contrast, a formula-fed baby is provided with 2.7 grams per kg per day of protein at usual intake volumes. Raiha has suggested that this protein intake may be excessive, citing higher plasma levels of blood urea nitrogen and branched-chain amino acids in formula-fed infants.[49] In an effort to simulate breast milk, many of the proprietary formulas now have adopted a whey:casein ratio closer to that of human milk (60:40). The whey provided in such formulas remains bovine in origin, however, with a different composition from that of human whey. Janas and colleagues compared amino acid patterns and urea nitrogen in the blood of term infants fed human milk, whey (bovine)-predominant formula or cow's milk formula.[50] Plasma values for several amino acids and blood urea nitrogen were higher in the infants fed both of the formulas compared with the infants fed breast milk. The plasma amino acid patterns were largely predicted by the amino acid composition of the milk or formula. The authors concluded that the whey-predominant formulas were not superior to cow's milk, that both formulas provided excessive quantities of amino acids and that the

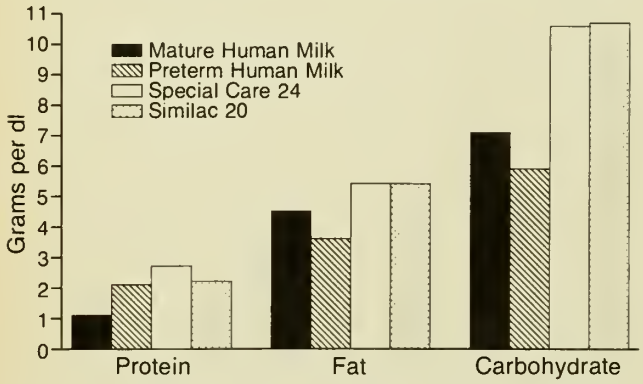

Figure 9.—The composition of the major nutrients in several representative oral nutrient sources is compared.

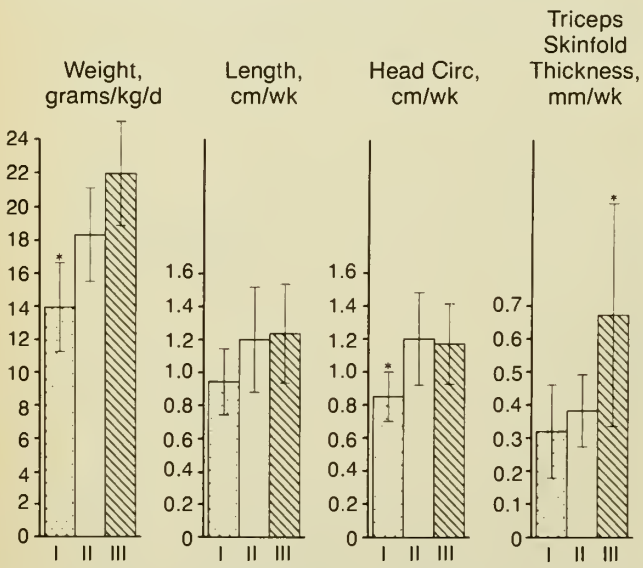

Figure 10.—The graphs show growth rates with varying protein and energy intakes. The protein intake has a major effect on promoting growth in preterm human infants. Additional calories add slightly to weight gain and significantly to triceps skinfold thickness, perhaps representing an increase in body fat. I (□) = protein 2.24 grams/kg/d, energy 115 kcal/kg/d; II (□) = protein 3.6 grams/kg/d, energy 115 kcal/kg/d; III (▧) = protein 3.6 grams/kg/d, energy 149 kcal/kg/d. *Significant difference, $P < .05$. Adapted from Kashyap et al.[52]

TABLE 2.—*Daily Intake Range Recommended for Growing Stable 2-Week-Old, 29-Weeks' Gestational-Aged Infants (Cow Milk-Based Formula)**

Nutrient	*Daily Intake*
Vitamin B_{12}	0.15 μg/100 kcal
Folate	15 μg/kg
Vitamin C	30 mg/100 kcal
Niacin	4 mg preformed/100 kcal
Thiamine	250 μg/100 kcal
Riboflavin	335 μg/100 kcal
Pyridoxine	250 μg/100 kcal
Vitamin A	1,400 IU
Vitamin E	25 IU†
Vitamin K	5 μg/kg
Vitamin D	400 IU
Iron	2 mg/kg by doubled birth weight‡
Calcium	Up to 200 mg/kg§
Phosphorus	Up to 113 mg/kg§
Magnesium	5 to 6 mg/kg
Sodium	3 to 8 mEq/kg‖ up to 3 weeks, then 1 to 3 mEq/kg¶
Potassium	1 to 3 mEq/kg
Chloride	3 to 8 mEq/kg**
Zinc	800 to 1,200 μg/kg††
Copper	100 to 200 μg/kg
Selenium	1.5 to 2.5 μg/kg
Manganese	10 to 20 μg/kg
Chromium	2 to 4 μg/kg
Molybdenum	2 to 3 μg/kg
Biotin	0.6 to 2.3 μg/kg
Pantothenic acid	1.0 to 1.4 mg/kg
Choline	5 to 9 mg/kg

*From Tsang.[51]

†25 IU/d is recommended to establish tissue vitamin E stores in the first 2 to 4 weeks; beyond that, 5 IU/d is satisfactory.

‡1 to 2 mg/kg/d before this time, if blood loss is not replaced.

§Low calcium and phosphorus concentrations in human milk fed to preterm infants result in low bone mineral content, which may be prevented by using mineral supplements. Preterm infants receiving exclusively human milk for prolonged periods should be examined, at least at 2 months of age, for rickets and fractures using x-ray films and measuring serum phosphorus and possibly alkaline phosphatase levels.

‖Decrease to 2 mEq/kg/d if the serum sodium level is more than 144 mEq/liter.

¶Increase again if serum sodium level is less than 132 mEq/liter.

**Can reduce to 1.0 mEq/kg if bicarbonate is given.

††Infants appear to be generally in negative balance even at these levels of intake.

protein content of such formulas should be reduced to achieve blood indices characteristic of human milk feeding.[50]

Commercial formulas for infants of low birth weight provide even greater amounts of protein, fat and carbohydrate (Figure 9, Table 2). At 150 ml per kg per day of intake, the protein intake is about 3.5 grams per kg per day with an energy intake of about 120 kcal per kg per day. Studies by Raiha in preterm infants suggested that such protein intakes were not associated with improved growth but resulted in more metabolic abnormalities—azotemia, hyperammonemia, metabolic acidosis and abnormal plasma amino acid patterns.[49] In contrast, a recent study by Kashyap and co-workers compared two levels of protein intake in preterm infants, showing improved weight gain, head growth and nitrogen retention with 3.6 grams per kg per day of protein compared with 2.24 grams per kg per day (Figure 10).[52] These infants also had higher albumin and prealbumin levels, suggesting improved protein nutrition. The infants receiving the higher protein intake had no adverse metabolic effects. These investigators also examined the effect of energy intake on protein use, comparing the higher protein formula at two levels of energy intake, 115 kcal per kg per day versus 149 kcal per kg per day. They found no improvement in protein use at the higher caloric intake, although these infants did show a greater weight gain primarily from more fat deposition. The authors concluded that for preterm infants the lower protein intakes are inadequate, the higher protein intakes improve growth and are well tolerated and provision of greater energy at the higher protein intakes does not enhance protein use.

Human milk has greater amounts of cysteine and taurine than cow's milk, which may be of significance for a preterm infant.[49] Taurine may be important in neural and retinal development and is synthesized suboptimally in premature babies. Commercial formulas are now supplemented with additional taurine. Cysteine is derived from methionine by the enzyme cystathionase, which may be relatively deficient in newborns. The higher cysteine and lower methionine content of breast milk compensates for this deficiency.

Breast milk protein composition differs between preterm and term milks, preterm milk containing more calories, fat, protein and sodium but less lactose, calcium and phosphorus than term or mature milk (Table 3).[53] The protein concentration of premature milk is greater than that of mature milk, but less than that of commercial formulas (Figure 9). Preterm milk protein, fat and salt concentrations gradually decrease with postnatal age and are similar to mature milk by four weeks postpartum. Balance studies have shown improved nitrogen retention and growth in premature infants fed preterm versus mature human milk,[54] but still slower and with persistent nutrient deficiencies—such as calcium and phosphorus—than in infants fed enriched formulas designed for preterm infants.

Administering amino acids intravenously. Amino acid sources in parenteral nutrition were originally protein hydrolysates. These have been replaced by crystalline amino acid mixtures, which have produced a lower incidence of hyperammonemia and metabolic acidosis. The ideal amino acid composition for premature infants is not known, but new intravenous amino acid formulations, such as TrophAmine by American McGaw, and Aminosyn-PF by Abbott, have been designed to produce plasma amino acid patterns similar to those of a breast-fed infant. As an example, TrophAmine has

TABLE 3.—*Milk and Formula Composition*

Nutrient/dl	*Mature Human Milk*	*Preterm Human Milk*	*Preterm Human Milk + Natural Care**	*Special Care**	*Similac 20**
Calories	73.0	64.0	73.0	81.0	67.0
Protein, grams	1.1	2.1	2.2	2.2	1.5
Fat, grams	4.5	3.6	4.0	4.4	3.6
Carbohydrate, grams	7.1	5.9	7.2	8.6	7.2
Calcium, mg	33.0	27.0	98.0	146.0	51.0
Phosphorus, mg	15.0	14.0	50.0	73.0	39.0
Magnesium, mg	4.0	3.2	6.6	12.0	4.1
Sodium, mg	16.0	54.0	46.0	41.0	22.0
Potassium, mg	51.0	57.0	85.0	114.0	81.0
Chloride, mg	39.0	89.0	80.0	73.0	51.0
Iron, mg	0.021	0.1	0.2	0.3	0.15
Zinc, mg	0.16	0.48	0.84	1.2	0.5
Copper, μg	25.0-40.0	78.0	140.0	203.0	61.0
Vitamin A, IU	190.0-240.0	250.0	400.0	552.0	203.0
Vitamin D, IU	2.2	2.2	61.0	122.0	41.0
Vitamin E, IU	0.2-0.7	0.27	1.6	3.2	2.0
Vitamin K, μg	2.0	2.0	6.0	10.0	5.4
Vitamin C, mg	4.3-5.0	5.2	18.0	30.0	6.0
Vitamin B_1, mg	0.014	0.014	0.11	0.2	0.07
Vitamin B_2, mg	0.037	0.037	0.27	0.5	0.1
Vitamin B_6, mg	0.011	0.011	0.11	0.2	0.04
Vitamin B_{12}, μg	0.05	0.046	0.25	0.45	0.17
Niacin, mg	0.15-0.18	0.18	2.1	4.1	0.7
Folic acid, μg	5.2	5.2	18.0	30.0	10.0
Pantothenic acid, mg	0.18-0.23	0.23	0.87	1.5	0.3
Osmolality, mosm/kg	300.0	300.0	300.0	300.0	290.0

*Ross Laboratories, Columbus, Ohio.

been shown to produce such an aminogram by including a high percentage of essential amino acids (60% versus 40% in most other intravenous amino acid mixtures), a relatively higher proportion of branched-chain amino acids (shown to promote a more positive nitrogen balance by specifically stimulating protein synthesis and by inhibiting protein catabolism), a balanced combination of nonessential amino acids rather than a disproportionate amount of glycine and the inclusion of cysteine (as an additive), taurine and tyrosine (as *N*-acetyl-L-tyrosine) (Table 4).[55] In a recent clinical trial of TrophAmine, all of the serum amino acid concentrations produced in a group of preterm infants were within the 95% confidence limit ranges of a group of healthy, term breast-fed neonates. A comparable group of infants receiving FreAmine III (American McGaw) had significantly but only slightly high levels of methionine, phenylalanine and glycine and significantly but only slightly low levels of tyrosine (Figure 11).[56] Additional information in this limited number of preterm, low-birth-weight infants receiving TrophAmine also suggested some improvement in weight gain and nitrogen retention compared with the FreAmine III group. On the other hand, as shown in Figure 11, the discrepancies between the plasma aminograms for TrophAmine and FreAmine III are quite small, and it seems difficult to reconcile the significant changes in growth and nitrogen balance with such small differences in amino acid balance. Further comparative trials of TrophAmine or similar formulations versus the more conventional amino acid mixtures given intravenously are needed to define more accurately and convincingly whether producing a modified aminogram improves growth of the very-low-birth-weight infant, who does or does not have specific illnesses. Further research is needed also to define the effect of selected plasma aminograms on the growth and development of specific tissues, particularly the neural tissues that have been shown to be uniquely altered or injured by "toxic" levels of certain amino acids such as phenylalanine and methionine, and the hepatobiliary system that in preterm infants, especially those not fed enterally, seems particularly sensitive to the development of cholestasis with a prolonged use of intravenous amino acids.

TABLE 4.—*Comparison of Intravenous Amino Acid Products**

Amino Acids	*TrophAmine*† 6%	*FreAmine III*† 6%
Essential		
L-Isoleucine	0.49	0.41
L-Leucine	0.84	0.63
L-Lysine	0.49	0.50
L-Methionine	0.20	0.32
L-Phenylalanine	0.29	0.34
L-Threonine	0.25	0.22
L-Tryptophan	0.12	0.08
L-Valine	0.47	0.37
L-Histidine	0.29	0.16
L-Cysteine	<0.02	<0.01
Taurine	0.015	0.00
L-Tyrosine (eq)	0.14	0.00
Nonessential		
L-Alanine	0.32	0.40
L-Arginine	0.73	0.53
L-Proline	0.41	0.63
L-Serine	0.23	0.33
L-Aspartic acid	0.19	0.00
L-Glutamic acid	0.30	0.00
Glycine	0.22	0.78

*Grams/dl.
†American McGaw, Irvine, Calif

Fat

Lipids are a major source of energy, fat-soluble vitamins, hormones and essential fatty acids for neonates. The essential fatty acids are important for cell membrane integrity as phospholipids and are precursors of prostaglandins and leukotrienes. Linoleic acid is the predominant essential fatty acid and provides 8% to 10% of the fat calories present in breast milk. Linolenic acid is a normal component of human milk (about 2% of fat calories) and thus forms normal parts of structural phospholipids, particularly in the myelin of growing neural tissue, in infants fed with milk. In contrast to linoleic acid, a true deficiency state for linolenic acid in human infants has not been documented clearly. Fats contribute about 50% of the total calories in breast milk or formula with a higher caloric value (9.45 kcal per gram). The lipid content of breast milk, however, is variable in concentration and composition depending on the phase of lactation—colostrum, transitional or mature milk—stage of pregnancy, time of day and time within a feeding. Fat concentrations are lowest in the morning and at the beginning of a feeding.[57]

Lipid digestion depends on lipase breakdown of triglycerides and bile salt emulsification of fats. Pancreatic lipase and bile salt levels are low in newborns, especially preterm infants. Compensatory mechanisms for lipolysis include lingual lipases and bile salt-stimulated lipase in breast milk. Lingual and gastric lipases are present at 26 weeks and increase substantially between 32 and 40 weeks of age. Bile salt-stimulated lipase is activated by bile salts in the duodenum and

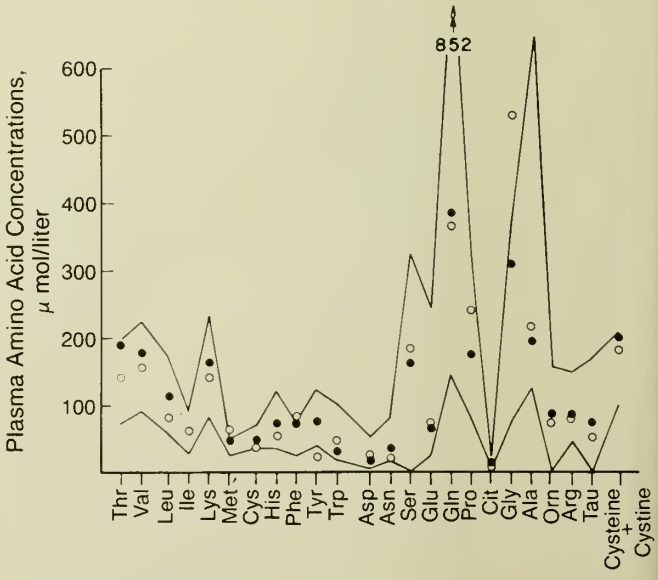

Figure 11.—The mean plasma amino acid concentrations in preterm infants fed intravenously with TrophAmine (•) or with FreAmine III (o) are compared with the 95% confidence limits of amino acid concentrations in term, breast-fed infants. Adapted from Helms et al.[56] Ala = alanine, Arg = arginine, Asn = asparagine, Asp = aspartic acid, Cit = citrulline, Cys = cysteine, Gln = glutamine, Glu = glutamic acid, Gly = glycine, His = histidine, Ile = isoleucine, Leu = leucine, Lys = lysine, Met = methionine, Orn = ornithine, Phe = phenylalanine, Pro = proline, Ser = serine, Tau = taurine, Thr = threonine, Trp = tryptophan, Tyr = tyrosine, Val = valine

facilitates fat absorption.[58,59] Cow's milk-based formulas contain vegetable fats that are largely hydrolyzed in the stomach. Fat absorption in term infants taking breast milk is 90% to 95% in the first month of life compared with 85% to 90% with formula feeding.

Following birth, ingestion of milk provides a dramatic increase in fat intake, even for those mammals (human, rabbit, guinea pig) whose fetuses received significant amounts of fat in utero. Furthermore, not only is fat intake increased dramatically, so also is fat oxidation. This increase in fat metabolism also can occur immediately after birth in those newborns with large white fat depots in response to the sudden postnatal surge in adrenalin and glucagon leading to fatty acid mobilization. This postnatal surge in fatty acid oxidation also is important for sustaining the rate of gluconeogenesis necessary to provide sufficient glucose for energy metabolism, principally in the brain, following the loss of umbilical glucose supply.[60,61]

Fat infusion. Intravenous lipid infusions have been used successfully in preterm infants for a number of years. Table 5 shows the composition of three commercial products. Several advantages of infusing lipid intravenously have been documented. Doses as low as 0.5 grams per kg per day prevent the development of essential fatty acid deficiency that occurs in almost all infants by the end of the first week of postnatal life when no fat is provided,[62] although it usually takes at least three to four weeks before clinical signs of essential fatty acid deficiency (dermatitis, growth failure) occur. Other potential problems from essential fatty acid deficiency include platelet aggregation abnormalities and an abnormal composition of pulmonary surfactant phospholipids that may lead to abnormal surfactant function.

With the substitution of fat for glucose, carbon dioxide production rates decrease because equal-caloric oxidation of fat produces less CO_2 than does glucose.[63] This effect is especially pronounced when fat infusion prevents lipogenesis from glucose, a very high CO_2-generating process. An increased CO_2 production rate may lead to an increased respiratory drive resulting in hyperventilation and a burdensome increase in the metabolic rate. Also, substituting the intravenous administration of fat for that of glucose may prevent the hyperglycemia characteristic of very small, stressed preterm infants, allowing an increased total energy intake. Finally, not the least significant result of parenteral fat administration is that the higher caloric density at no significant increase of an osmolar load allows many infants to be fed by the safer peripheral venous approach rather than by highly complicated central venous catheters necessary for high-osmolar glucose infusions.

Intravenous fat infusion has not been used without significant side effects. Large boluses of lipid given intravenously have decreased pulmonary oxygen diffusion,[64] and very high infusion rates (>4 grams per kg per day) have been associated with decreased blood oxygen levels in preterm infants.[65] Even at modest rates of intravenous lipid infusion, however, autopsy studies have shown excessive lipid deposits in the lungs of these infants compared with orally fed infants.[66] Such lipid deposition was related primarily to the total amount of fat infused over time. Additionally, some studies have noted abnormal leukocyte function in the presence of lipid emulsions,[67] and lipid deposits occur in reticuloendothelial cells, although there is not yet an established immune deficiency that develops from these reticuloendothelial-lipid deposits. At high levels of fatty acid infusion, bilirubin can be displaced from albumin, although this process may not be significant unless a very high bilirubin-to-albumin molar ratio exists (for example, a bilirubin level of more than 10 mg per dl or a serum albumin level of less than 2.0 grams per dl, or both) or the infant is notably immature, in which case fatty acid metabolism is much slower due to such factors as a relative carnitine deficiency, inadequate activation or amount of lipoprotein lipase or other factors.[68] Finally, both modest and high doses of fat given intravenously (3 to 8 grams per kg per day) have caused increased prostaglandin production (especially thromboxane) with evidence of pulmonary hypertension,[64,69,70] and intravenous fat mixtures with an excess or deficiency of one series of prostaglandin fatty acid precursors may in turn lead to a deficiency or excess of the corresponding prostaglandin series.[71] For example, excess linolenic acid may inhibit the conversion of linoleic acid to arachidonic acid, a process observed in vitro but not yet in vivo. Consequences of "abnormal" structural phospholipid composition that can result from unusual mixes of various fatty acids are not known. Because essential fatty acids form a significant portion of such vital membranes as the myelin sheaths of developing central nervous system neurons, achieving "normal" structural composition of such membranes seems a valuable goal. Thus, as with formulas, the tendency for the manufacturers of proprietary intravenous fat mixtures has been to approximate the fatty acid pattern of human milk in their intravenous fat products.

TABLE 5.—*Distribution by Percent of Fatty Acids in Intravenous Fat Emulsions*

Fatty Acid	*Intralipid**	*Liposyn†*	*Travamulsion‡*
Linoleic	54	77.0	56
Linolenic	8	0.5	6
Oleic	26	13.0	23
Palmitic	9	7.0	11
Stearic	3	2.5	? 4

Glycerin + egg phospholipid.1.1 kcal/ml

*KabiVitrum, Inc, Alameda, Calif.
†Abbott Laboratories, No Chicago, Ill.
‡Travenol Laboratories, Inc, Deerfield, Ill.

Practically, little evidence of such potential difficulties has been observed at intravenous lipid infusion rates of 0.5 to 1.0 grams per kg per day, and essential fatty acid deficiency appears prevented at this infusion rate. Higher rates produce a greater caloric advantage but should be approached cautiously. Finally, there is no evidence that fat should be given intravenously when oral feedings are adequate.

Vitamins, Minerals and 'Special Supplements'

Requirements for vitamins and minerals in premature infants have been reviewed recently and are included in Table 2.[51] Many of these requirements were rather imprecisely estimated by extrapolating data obtained in older infants. With the possible exception of vitamin D, milk appears to provide adequate vitamin levels at normal intake rates (in fact, calcium and phosphorous supplements may be more important than vitamin D for promoting adequate bone mineralization). In general, all formulas provide adequate to excessive vitamin intakes, and there appears to be no advantage to the common practice to supplement infants' diets with multivitamin preparations. In fact, supplementing the special formulas for pre-

mature infants with extra vitamins may be dangerous. Also, milk or formula intake volumes must be considered as important as the concentration of vitamins in the milk or formula when estimating vitamin dosages.

A recent review of vitamin levels in preterm infants fed intravenously showed that recommended dosages were adequate to prevent deficiency, but several vitamin levels were elevated above the reference range (pantothenate, biotin, vitamin B_{12}, ascorbic acid).[72,73] Further studies are needed to define optimal vitamin intakes, especially in premature infants.

Regarding trace elements, zinc, copper and iodine requirements are best defined with respect to preventing clinically significant deficiencies—growth failure with zinc deficiency, anemia with copper deficiency, hypothyroidism with iodine deficiency. Manganese and selenium have been added to these three trace elements in neonatal trace element supplements for total intravenous nutrition, although there are little hard data on which to base the dose of manganese and selenium supplements. Iron is usually withheld until six to eight weeks postnatally when iron stores are diminished and to prevent iron oxidant-induced hemolytic anemia and iron-related gut bacterial overgrowth.

Regarding macroelements, sodium supplementation for preterm infants is important because of higher urinary losses and the dependence of growth on a normal sodium intake. These intakes of sodium should be carefully measured by intake and output analyses. Excessive sodium intake, particularly later in infancy, may lead to hypertension. Calcium and phosphorus accretion in late gestation is estimated at 300 mg per day and 150 mg per day, respectively.[2] Actual requirements in preterm infants must be carefully measured due to varying intestinal absorption (better from milk than from formula), urinary excretion (affected by renal disease, renal maturity and diuretic therapy) and parathyroid and vitamin D functional capacity. Although nearly maximally supplemented with calcium and phosphorus, the special formulas for premature infants still may not provide enough of these elements to prevent the failure of bone mineral content to follow bone growth and the development of biochemical rickets in a rapidly growing preterm infant.[74] On the other hand, rickets is uncommon to nonexistent in milk- or formula-fed older infants who receive a normal intake of vitamin D.

Carnitine is an additional nutrient that is necessary to transport long chain fatty acids into the mitochondria where oxidative metabolism can take place. Carnitine is a normal constituent of human milk and has been added to most formulas with some evidence of improved fat oxidation.[75] Carnitine levels are low in preterm infants fed intravenously, but intravenous supplementation can produce normal carnitine levels in such infants.[76] The metabolic effects of intravenous carnitine supplementation to intravenously fed infants need further investigation, but at least one preliminary trial suggests that lipid oxidation and lipid metabolism can be increased with intravenous carnitine supplementation.[77]

Extreme caution should be used when evaluating each new special supplement, whether it appears to be a new "essential" amino acid, such as taurine or cysteine, or an exciting therapeutic item. For example, inositol has received interest for its possible potential to enhance surfactant production[78]; vitamin A may ameliorate bronchopulmonary dysplasia,[79] and vitamin E has been used to protect against oxidant-induced hemolytic anemia,[80] retrolental fibroplasia[81] and bronchopulmonary dysplasia.[82] On the other hand, sugar alcohols such as inositol can be toxic and vitamin A toxicity can be significant with intracranial hypertension. Furthermore, each of the vitamin E uses has its critics or has not worked out well in clinical trials,[83] although the prevention of hemolytic anemia is on soundest ground. Finally, as one further example, selenium has been added to trace element mixtures but, at "higher doses" (what dose is too high in preterm infants is not known precisely), selenium may produce growth retardation through reduction of growth hormone and somatomedin-C production.[84]

Milk and Formula Composition

As previously discussed, breast-fed term infants provide the standard for growth and dietary intake for normal neonates. Preterm infants have different requirements, based on intrauterine growth rates and body composition. Breast milk and several commercial formulas are compared in Table 3. Preterm breast milk contains higher amounts of protein and sodium than mature milk. Preterm infants, however show improved growth and mineral balance when fed with fortified preterm milk or one of the formulas developed for such infants. There are several formulas for preterm infants available, but they share certain characteristics when compared with mature human breast milk. Such formulas contain more protein, calcium, phosphorus and sodium. The carbohydrate source is a combination of glucose polymers and lactose. The fats include vegetable oils and medium-chain triglycerides (MCTs) that are more easily absorbed from the intestinal lumen because they do not require bile salts. Also, MCTs do not appear to require carnitine for transport into mitochondria. The preterm infant formulas also contain larger amounts of vitamins and trace minerals. The improved growth in preterm infants fed such formulas is probably due primarily to the greater protein and mineral content (Figure 9).

Because of the clinically apparent inadequacy of mature human milk to provide enough protein and minerals for "normal" growth of preterm infants, most neonatologists are starting to add special dietary supplements to milk when these infants are exclusively fed mature human milk. Two commercial supplements are available: Human Milk Fortifier (Mead Johnson, Evansville, Ind), a powder of whey, casein, corn syrup solids and minerals, containing 14 kcal per four packets (for 100 ml of milk), 20% protein, 77.4% carbohydrates and 2.6% fat; and Natural Care (Ross Laboratories), a liquid of whey, casein, lactose, corn syrup solids, medium-chain triglycerides, corn and coconut oil, minerals, trace elements and vitamins, containing 0.81 kcal per ml, 11% protein, 40% carbohydrate and 49% fat. Also, Polycose, described earlier; MCT Oil (Mead Johnson), a mixture of medium-chain triglycerides, and powdered and liquid formulas are always available to mix with milk. Clinical trials in preterm infants have not shown increased growth with MCT Oil or Polycose supplementation of mature milk, but supplements of Human Milk Fortifier, Natural Care and formulas have resulted in more rapid growth, presumably related to the additional protein supplement.[85]

Summary

In this review we have focused on metabolic requirements for fetal and neonatal nutrition. The two major reasons for this focus are to provide insight into the current knowledge about nutrient requirements and to suggest that there is still a great

deal of basic information to be gained from research to help put nutrition of fetuses and preterm infants on a more rational, scientific basis. Much of this sort of research has been and is being done. But problems generated by too hasty a clinical trial or an emotionally biased mind-set continue to crop up. Examples include the tragic neonatal outcomes in some infants given a harmful preparation of vitamin E that had not been adequately tested,[86] the development of clinical rickets in some exclusively breast-fed (with "mature" milk) preterm infants and the considerable morbidity—and occasional mortality—associated with the frequently trial-and-error and occasionally cavalier approach to intravenous nutrition.

Thanks to the development of artificial surfactant and prenatal and postnatal enhancement of surfactant production, prevention and cure of the respiratory distress syndrome is a near reality. For a large percentage of preterm infants, we will no longer have to say "He (or she) is too sick to feed." Perhaps this group of infants will provide a special impetus for increased investigation into and improved knowledge of the nutritional requirements of all infants.

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Medical Staff Conference

Diabetes, Dietary Protein and Glomerular Hyperfiltration

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Despite the availability of insulin for the prevention and treatment of the metabolic abnormalities in diabetes mellitus, microvascular complications involving the eye, kidney and nervous system develop in many patients with this disorder. Diabetic nephropathy, in particular, represents one of the major causes of morbidity and mortality facing patients with this disease. Drs Burl Don and Morris Schambelan will discuss the current understanding of the pathogenesis of diabetic nephropathy and other forms of chronic renal disease and potential therapeutic approaches that may retard or prevent their progression.*

BURL R. DON, MD,† and MORRIS SCHAMBELAN, MD‡: Recently a series of provocative clinical and experimental observations has identified several pathophysiologic states in which the glomerular filtration rate (GFR) is supernormal. This phenomenon (called "glomerular hyperfiltration") and an associated increase in the glomerular transcapillary hydraulic pressure difference ("glomerular hypertension") occur in disorders such as diabetes mellitus[1-5] and in remnant nephrons following subtotal nephrectomy[6] and are modified by alterations in certain dietary constituents, particularly protein.[7,8] Although this increase in GFR has sometimes been thought to be a useful adaptation, particularly after the loss of functioning renal mass, there is a growing body of evidence suggesting that such altered glomerular hemodynamics may be deleterious to renal function by initiating a pathogenetic sequence that eventuates in anatomic damage and proteinuria (Figure 1).[9-11]

The mechanisms by which the increases in GFR and proteinuria occur are largely unknown. We will review the evidence that suggests that abnormalities of glomerular eicosanoid production occur and play a pathophysiologic role in states associated with glomerular hyperfiltration and hypertension. Particular emphasis will be given to studies done in patients and experimental animals with diabetes mellitus, inasmuch as this is the prototypic disorder that is characterized by these glomerular hemodynamic abnormalities. In addition, we will also review data that suggest that glomerular eicosanoids may play a role in the glomerular hemodynamic changes that occur following a reduction in functioning renal mass and in response to an alteration in dietary protein intake. Finally, we will consider the role of the renin-angiotensin system and of the interaction between angiotensin II and glomerular eicosanoids in the pathogenesis of glomerular hyperfiltration.

Abnormalities of Glomerular Function in Diabetes Mellitus

Abnormalities of glomerular function are prominent features of diabetes mellitus. In approximately 40% of patients with type I (insulin-dependent) diabetes and in a somewhat smaller percentage of persons with type II (non-insulin-dependent) diabetes, diabetic nephropathy will develop, characterized by proteinuria, a loss of renal function and a rapid progression to end-stage renal failure.[12] The clinical features and pathogenesis of this important cause of chronic renal insufficiency were reviewed recently in this forum[13] and elsewhere.[14]

Before the onset of overt clinical diabetic nephropathy and progressive renal insufficiency, many persons with diabetes, particularly those with type I diabetes who were studied early in the course of their disease, have had a supernormal GFR and renal plasma flow (Figure 2).[15,16] Retrospective analysis of the subsequent course in such patients suggests that such hemodynamic abnormalities, together with the presence of microalbuminuria and systemic hypertension, may herald the subsequent development of diabetic nephropathy.[17]

That some component of the metabolic derangement in diabetes is responsible for the alterations in glomerular hemodynamics is evidenced by the observation that "tight control" with insulin will prevent or correct the hyperfiltration in both patients with clinical diabetes mellitus[18-20] and in animals in which diabetes is induced experimentally with streptozocin (streptozotocin).[21] Structural hypertrophy, typically seen in kidneys of diabetic patients and animals,[22] may account in part for these findings. Indeed, the increased GFR and renal plasma flow correlate with renal size in patients with type I diabetes.[15,23] In diabetic rats a pronounced increase in renal weight and cellular hypertrophy can be detected within the first 24 hours after the onset of hyperglycemia.[22]

Hyperglycemia per se may play a role as evidenced by the increase in GFR that occurs with infusion of glucose in both normal subjects and in persons with insulin-dependent diabetes[24] and by the reduction in the elevated levels of GFR and renal plasma flow in type I diabetes that results when glucose levels are normalized by short-term, intense insulin therapy.[25]

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
ANP = atrial natriuretic peptide
GFR = glomerular filtration rate
HPLC = high-performance liquid chromatography
PG = prostaglandin
TX = thromboxane
UCSF = University of California, San Francisco

In addition to hyperglycemia, the diabetic state is characterized by increased circulating levels of glucoregulatory hormones such as glucagon and growth hormone, both of which can induce an increase in the GFR.[26-28]

The pathogenesis and pathophysiologic significance of glomerular hyperfiltration in diabetic nephropathy have been elucidated further in studies done in rats with experimentally induced diabetes mellitus. Similar to the findings in humans with type I diabetes, the whole-kidney GFR is increased 30% to 40% above control in rats made diabetic with the β-cell toxin streptozocin.[4] The determinants of GFR in this model have been assessed using the technique of free-flow micropuncture. Such studies in Munich-Wistar rats have identified the major physical determinants of the GFR: glomerular plasma flow, afferent protein concentration, transcapillary hydraulic-pressure difference and the glomerular capillary ultrafiltration coefficient.[29] These micropuncture studies indicate that, in diabetic rats, the single-nephron GFR and glomerular capillary plasma flow are increased as a consequence of renal vasodilatation.[4] In addition, the transglomerular capillary pressure difference is increased.[4] Such glomerular hypertension appears to play a critical role in the initiation and progression of diabetic nephropathy. This concept stems from the observation that, before inducing diabetes mellitus in rats, a unilateral reduction in renal perfusion pressure due to placing a clip across one renal artery attenuated the subsequent development of diabetic nephropathy in the "clipped" kidney.[30] Similarly, the occurrence of a unilateral atherosclerotic plaque in a renal artery of a diabetic patient[31] protected the ipsilateral kidney from diabetic nephropathy, whereas the contralateral kidney with a patent renal artery showed Kimmelstiel-Wilson lesions. Furthermore, despite persistent hyperglycemia, glomerular damage and proteinuria in rats can be prevented by maintaining intraglomerular pressures at normal levels using either dietary[8] or pharmacologic means[32] (discussed later). Thus, the degree of intraglomerular hypertension appears to be more important than the metabolic derangement in the pathogenesis of diabetic nephropathy.

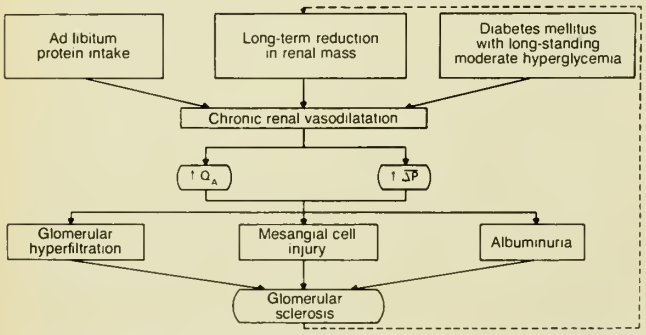

Figure 1.—Summary of the hypothesis of Brenner and associates that indicates a role for sustained increases in glomerular pressures and flows in the initiation and progression of glomerular damage. In this model it is proposed that ad libitum protein intake, reduction in renal mass and diabetes mellitus all lead to renal vasodilatation as reflected by an increase in glomerular capillary plasma flow rate (Q_A), and an increase in glomerular transcapillary hydraulic pressure (ΔP). The resulting loss of functioning nephrons sets up a vicious cycle (dashed line) whereby the reduction in renal mass leads to further hyperfiltration and eventual destruction of the remaining functioning nephrons. (Reprinted with permission from Brenner.[11])

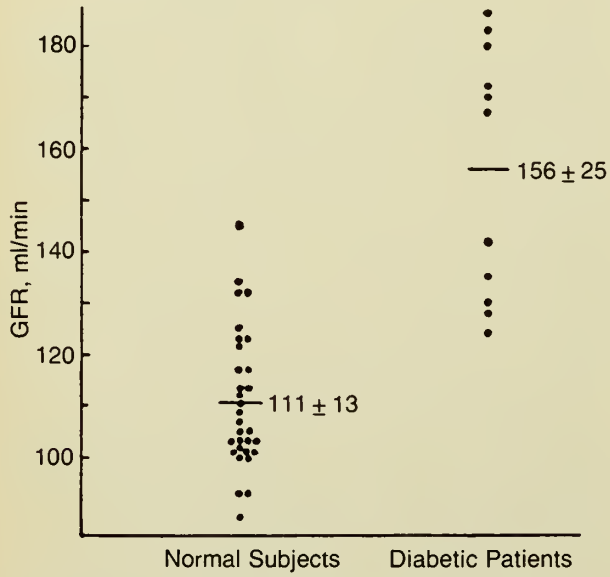

Figure 2.—Comparisons of measurements of the glomerular filtration rate (GFR) in 11 patients with untreated type I diabetes mellitus and 31 normal subjects. The difference between groups was significant ($P < .001$). (Reprinted with permission from Mogensen.[2])

Abnormalities of Glomerular Eicosanoid Metabolism in Diabetes Mellitus

It has been suggested that abnormalities of vasoregulatory hormones may play a role in the pathogenesis of glomerular hyperfiltration.[8] Several classic circulating hormones, such as parathyroid hormone and vasopressin, and other biologic messengers that are produced in the kidney and that act locally through an autocrine or a paracrine mechanism—eicosanoids, angiotensin II—can affect the GFR.[33] In addition to vasoactive effects on the afferent and efferent renal arterioles with subsequent alteration of renal vascular resistance, many of these substances affect the filtration process by a reduction in the glomerular capillary ultrafiltration coefficient, an action that appears to be mediated by contraction of the glomerular mesangial cell and reduction of the glomerular capillary surface area. This may be due to a direct contractile effect of the agonist on the mesangial cell, as in the case of angiotensin II and vasopressin, or by secondary activation of the renin-angiotensin system.[33,34] Prostaglandins, which are secreted by whole glomeruli[35-37] and by cultured glomerular mesangial cells,[38-40] can influence the GFR by modifying the vasoconstrictor effects of angiotensin II[41] and the glomerular contractile response to this agonist.[42]

To evaluate directly the effect of diabetes mellitus on glomerular eicosanoid metabolism, we did studies in the early stages of an experimental model of diabetes mellitus in rats.[43] Control rats, which were matched for age and weight at the time of intravenous administration of streptozocin, received an equal volume of the vehicle. The onset of diabetes was manifested by the development of polyuria and polydipsia within two to three days of administering streptozocin. Substantial hyperglycemia occurred promptly in the rats that re-

ceived streptozocin and tended to increase further during the subsequent weeks of observation.

Studies of eicosanoid metabolism were done 9 to 23 days after administering streptozocin. Glomeruli were isolated by mechanical sieving. Eicosanoid production was evaluated both by direct radioimmunoassay and by identification of labeled products by high-performance liquid chromatography (HPLC) after incubation with arachidonic acid labeled with carbon 14. Glomerular prostaglandin (PG) production was increased in diabetic rats. In studies done in individual rats, the mean production rates of both PGE_2 and $PGF_{2\alpha}$, the major prostaglandins produced by rat glomeruli, were approximately twofold greater in the rats with diabetes, whereas those of thromboxane (TX) B_2 were not significantly greater than of controls (Figure 3). PGE_2 production was also measured on the supernatant obtained from incubating pools of glomeruli from diabetic and control rats. In these studies, the mean basal PGE_2 production was also about twofold greater in glomeruli from diabetic animals. When metabolism of arachidonic acid ^{14}C was evaluated by HPLC, conversion to labeled PGE_2, $PGF_{2\alpha}$ and TXB_2 and hydroxyheptadecatrienoic acid by diabetic glomeruli was twofold to threefold greater compared with that in control glomeruli, whereas no significant difference in conversion to 12- and 15-hydroxyeicosatetraenoic acid occurred. These findings indicate that glomerular cyclooxygenase but not lipoxygenase activity was increased in the diabetic animals.

The increased rate of prostaglandin production did not appear to be due to a nonspecific effect of streptozocin inasmuch as glomerular prostaglandin production was not increased significantly in streptozocin-treated rats made euglycemic with insulin therapy. The increased rate of prostaglandin production also did not appear to be related directly to the severity of the diabetic state as reflected by the degree of hyperglycemia at the time of death. In fact, the rates of glomerular prostaglandin production in the individual diabetic animals correlated inversely with the plasma glucose concentration.

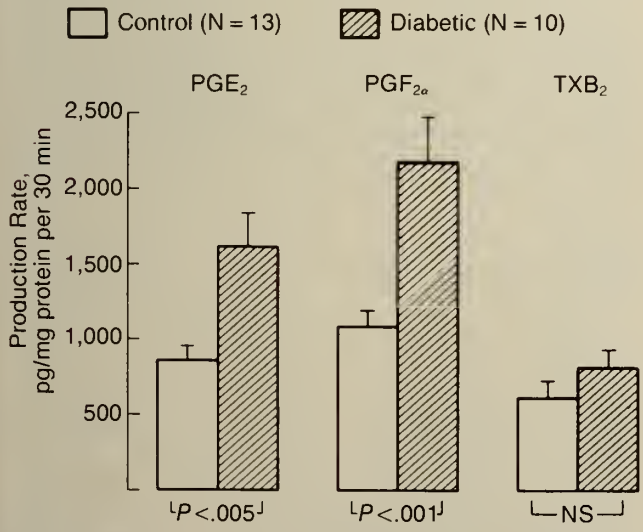

Figure 3.—Comparison of eicosanoid production by glomeruli isolated from rats with streptozocin-induced diabetes mellitus and control animals. Production rates were assessed by direct radioimmunoassay of the supernatant after incubating the glomeruli for 30 min at 37°C. Production rates for both prostaglandin (PG) E_2 and $PGF_{2\alpha}$ were twofold greater in the diabetic animals, whereas the production of thromboxane (TX) B_2 was not significantly (NS) greater than in controls. (Adapted from data in Table 1 in Schambelan et al.[43])

Similar increases in glomerular prostaglandin synthesis in diabetic rats have now been reported by other investigators.[44,45] Taken together with the results of our study, it appears that, at least in the early stages of the disorder, glomerular prostaglandin synthesis is increased in glomeruli from diabetic rats.

The functional significance of this augmented production of glomerular prostaglandins observed in diabetic animals is suggested by studies using cyclooxygenase inhibitors as pharmacologic probes of the renal circulation. Treatment with cyclooxygenase inhibitors—indomethacin, acetylsalicylate—prevented glomerular hyperfiltration when administered in the early stages of experimental diabetic nephropathy in rats,[45,46] reduced intraglomerular hypertension[47] and prevented the progressive decrease in the GFR characteristic of the chronic stages of this model.[46] Although studies evaluating the effect of long-term treatment with cyclooxygenase inhibitors in humans with glomerular hyperfiltration have not been reported, short-term infusion of lysine acetylsalicylate significantly reduced the supernormal GFR and renal plasma flow in patients with type I diabetes mellitus.[48]

Abnormalities of Glomerular Function Following a Reduction in Renal Mass

As renal mass is reduced, the remaining nephrons increase in size and function. Studies in dogs[49] and in rats[50] have shown that glomerular hyperfiltration occurs following partial renal ablation, and the degree of this functional adaptation correlates with the amount of renal mass removed. Deen and co-workers[6] found that the single-nephron GFR was increased in remnant nephrons from rats with partial renal ablation. Similar to the glomerular hemodynamic profile that occurs in rats with streptozocin-induced diabetes mellitus, the determinants of this elevated single-nephron GFR were noted to be an increase in the glomerular transcapillary hydraulic pressure gradient and glomerular plasma flow rate, occurring as a consequence of glomerular arteriolar vasodilatation. Such altered glomerular hemodynamics result in progressive azotemia, proteinuria and glomerulosclerosis. In 1932 Chanutin and Ferris[51] reported that proteinuria, hypertension and progressive dysfunction occurred in rats subjected to three-quarters renal ablation. Studies by Shimamura and Morrison[52] and by Olson and associates[53] have documented that progressive histologic changes occur in remnant nephrons following subtotal nephrectomy, which include fusion of epithelial foot processes, expansion of the mesangium, collapse of the capillary lumen and subsequent focal and segmental glomerular sclerosis. Ultrastructural changes have been shown as early as one week after partial renal ablation.[53] Thus, functioning remnant nephrons, which augment their filtration and plasma flow as an apparent compensatory measure, undergo an acceleration of their own destruction following renal injury.

Effect of Partial Renal Ablation on Glomerular Eicosanoid Metabolism

The concept that vasodilatory prostaglandins may mediate an elevated single-nephron GFR and glomerular capillary plasma flow rate in functioning remnant nephrons is not surprising inasmuch as inhibition of renal prostaglandin synthesis in several experimental and clinical renal diseases results in a reduced renal blood flow and GFR.[54] We and other investigators have shown that glomerular production of

PGE_2, the major vasodilatory eicosanoid produced by the rat glomerulus, is greater in rats with partial renal ablation as compared with controls having a sham operation.[55] Inhibition of cyclooxygenase activity with indomethacin significantly reduced the GFR in rats with partial renal ablation, but not in control rats.[55] Similarly, recent micropuncture studies have shown that reducing renal prostaglandin production with indomethacin attenuated the augmented single-nephron GFR in rats with subtotal nephrectomies, whereas this therapy had no effect on the glomerular microcirculation in sham-operated controls.[56] These studies at both the whole-kidney and single-nephron level suggest that renal prostaglandin production plays an important role in the augmented renal hemodynamic response to partial renal ablation. Thus, like diabetes mellitus, rats with partial renal ablation may share a common dependency on renal eicosanoid biosynthesis in mediating glomerular hyperfiltration.

Role of Dietary Protein Intake in the Progression of Renal Disease

An increasing body of evidence supports an important role for dietary protein intake in the pathogenesis of glomerular hyperfiltration and the progression of renal insufficiency.[57] Several investigators in the 1920s to 1940s noted the deleterious effect of a high-protein intake in accelerating the progression of renal disease and recommended a reduction in protein intake in patients with chronic renal disease for the purpose of reducing the "workload" of the functioning nephrons.[58] Although restriction of dietary protein intake had long been recognized to reduce the symptoms of uremia and thus to play an important role in the conservative management of this disorder, with the advent of dialysis in the 1950s and 1960s, less attention was paid to the possible role of dietary therapy in retarding the progression of renal disease. Hostetter and colleagues[7] more recently showed an important link between dietary protein intake, altered glomerular hemodynamics and subsequent renal damage. Following partial renal ablation, glomerular hyperfiltration and hypertension failed to develop in rats fed a low-protein (6%) diet, whereas animals fed standard rat chow (containing 24% protein) showed typical elevations in single-nephron GFRs and glomerular hydraulic pressure (Figure 4). Additionally, prevention of glomerular hyperfiltration and hypertension by restricting protein intake was associated with preservation of normal glomerular histology. This important effect of dietary protein on glomerular hemodynamics has also been observed in normal rats: Ichikawa and co-workers[59] noted a decrease in the glomerular capillary plasma flow in rats fed a low-protein diet. Further, short- and long-term protein loads increase the GFR and renal plasma flow in both normal human subjects[60,61] and in experimental animals.[62,63] The clinical relevance of these observations has been supported by several studies that have evaluated the role of dietary protein restriction on the progression of renal disease in humans. For example, Maschio and associates[64] have shown that restricting the dietary protein intake in patients with early renal insufficiency greatly slowed the rate of deterioration of their renal function (Figure 5). Similar salutary effects on renal function have been achieved by Mitch[65] using low-protein diets supplemented with essential α-ketoanalogues.

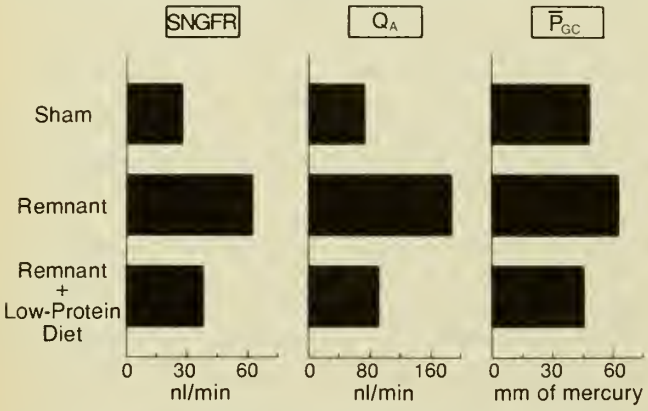

Figure 4.—Single-nephron glomerular filtration rate (SNGFR), glomerular capillary plasma flow rates (Q_A) and glomerular capillary hydraulic pressures ($\bar{P}_{GC}$) in rats with remnant nephrons following subtotal nephrectomy and sham-operated controls. Subtotal nephrectomy results in an augmentation in SNGFR, Q_A and $\bar{P}_{GC}$ in rats having a standard (24%) protein intake. Reducing dietary protein intake from 24% to 6% blunted these renal hemodynamic increases in the rats with remnant nephrons to levels observed in the sham-operated controls. Further, dietary protein restriction was associated with a preservation of normal glomerular histology and a decrease in proteinuria in the animals with subtotal nephrectomies. (Adapted from data in Table 1 with permission from Hostetter et al.[7])

Effect on Glomerular Eicosanoids of Varying Dietary Protein Intake

We have undertaken studies to determine the effect of varying the dietary protein intake on glomerular eicosanoid production in rats with Heymann nephritis. This is an immunologically mediated renal disease with many similarities to human membranous glomerulopathy. Heymann nephritis was induced by the intraperitoneal injection of FX1A antiserum.[66] Two days following induction of the model, an equal number of rats from each paradigm was randomly selected to receive either a high (40% casein)- or low (8.5% casein)-protein diet. The two diets were rendered isocaloric by adjusting the sucrose and dextrin contents. Dietary protein intake modulated glomerular prostaglandin production in these animals. Production rates of PGE_2, $PGF_{2\alpha}$ and TXB_2 were all significantly greater in glomeruli isolated from the rats with Heymann nephritis fed the high-protein diet in comparison to rats fed the low-protein diet. The degree of albuminuria was also greater in the rats ingesting the high-protein diet. A similar modulation of glomerular eicosanoid production by dietary protein intake has also been shown to occur in preliminary

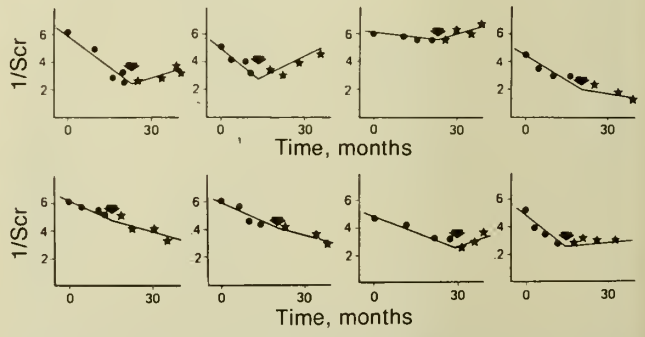

Figure 5.—Plot of the reciprocal of serum creatinine concentration as a function of time in 8 patients with chronic renal insufficiency before **(closed circles)** and after **(stars)** instituting dietary protein restriction **(arrows)**. The difference between the mean values of the slopes before (−0.0132) and after (−0.0013) protein restriction was significant ($F = 6.57$, $P < .01$). Thus, the rate of deterioration of renal function was attenuated by dietary protein restriction. (Reprinted with permission from Maschio et al.[64])

studies done in diabetic rats, rats with partial renal ablation and in normal animals.[67]

Several lines of evidence implicate renal eicosanoids in the increases in GFR and renal plasma flow that occur with protein intake in both humans and experimental animals. Renal production of eicosanoids is augmented following protein loading as reflected in the increased urinary excretion of PGE_2 with amino acid infusions in normal humans[68] and the elevated urinary PGE_2 and 6-keto-$PGF_{1\alpha}$ excretion following the ingestion of a high-protein diet in patients with chronic glomerular diseases.[69] The increase in GFR and renal plasma flow that occurs in response to infusions of arginine[70] or amino acid mixtures[68] or ingesting a meat meal[71] in normal human subjects can be blunted by pretreatment with cyclooxygenase inhibitors. Similar observations have been noted in rats with experimental renal disease and in normal animals. For example, urinary excretion of 6-keto-$PGF_{1\alpha}$ and PGE_2 was increased in normal rats on a long-term high-protein diet.[72] Further, pretreatment with indomethacin blocked both the increase in GFR and glomerular production of PGE_2 and 6-keto-$PGF_{1\alpha}$ that occurred in response to a short-term protein load.[73] Indomethacin treatment also prevented both the short-term increase in the GFR following a protein bolus in uremic rats[73] and the parallel increases in GFR and urinary excretion and glomerular production of 6-keto-$PGF_{1\alpha}$ associated with long-term ingestion of a high-protein diet in rats with Adriamycin (doxorubicin hydrochloride) nephrosis.[74]

The Renin-Angiotensin System and Glomerular Hypertension

The renin-angiotensin system has been implicated in the alteration in glomerular function that occurs in animals with various renal diseases. Anderson and colleagues[75] found that the angiotensin-converting enzyme (ACE) inhibitor, enalapril, was not only effective in treating the systemic hypertension following partial renal ablation in rats but, in addition, lowered the glomerular transcapillary hydraulic pressure. Furthermore, treatment with enalapril significantly limited the development of proteinuria and glomerular lesions. These investigators subsequently showed a therapeutic advantage of ACE inhibitors in retarding the progression of renal disease as compared with a standard antihypertensive regimen—reserpine, hydralazine hydrochloride and hydrochlorothiazide.[76] Whereas both enalapril and the standard antihypertensive therapy were effective in lowering systemic blood pressures in rats with partial renal ablation, only enalapril was effective in lowering the glomerular transcapillary hydraulic pressure and in limiting progressive proteinuria and glomerular damage.[76] Thus, control of the systemic blood pressure was inadequate in preventing progressive renal damage unless glomerular capillary pressure was also reduced. A similar beneficial effect of ACE inhibitor therapy in reducing the glomerular capillary pressure and preventing renal damage occurs in diabetic rats.[32] Treatment with angiotensin-converting enzyme inhibitors also reduced established proteinuria in rats with Heymann nephritis[77] and in patients with diabetes mellitus.[78] In addition, there has been a recent observation that ACE inhibitor therapy reduces the rate of deterioration of the GFR in patients with diabetic nephropathy.[79]

The advantage of therapy with an ACE inhibitor is probably related to its unique effect to decrease efferent arteriolar resistance,[75] possibly by reversing the preferential effect of angiotensin II on efferent arterioles.[80] This results in a reduction of glomerular capillary hydraulic pressures. Despite the "normalization" of glomerular pressures and protection against renal damage, therapy with enalapril did not lower the single-nephron GFR or glomerular plasma flow rate in rats with partial renal ablation and diabetes mellitus. Thus, it appears that glomerular hypertension rather than hyperfiltration is the factor responsible for glomerular injury.

The quantity of protein in the diet may also be a determinant of the activity of the renin-angiotensin system, as reflected by the levels of renin in the systemic circulation. In normal rats ingesting a high-protein diet, plasma renin activity was about threefold greater than in animals fed a low-protein diet.[72] Similar results have been observed in patients with chronic glomerular diseases. In such patients, the plasma renin activity was twofold greater while they ingested a high-protein diet than when they were maintained on a low-protein diet[69] and increased abruptly following the ingestion of a large protein meal.[81] That the renin-angiotensin system plays a role in modulating glomerular function by dietary protein is suggested by the observation that the salutary effect of a low-protein diet in reducing both glomerular capillary pressures and renal injury in experimental renal disease can be duplicated by ACE inhibitor therapy.[32,75] This is in accord with our recent observation that treatment with enalapril completely prevented the increment in urinary albumin excretion that occurred as a result of consumption of a high-protein diet in rats with Heymann nephritis.[77] Because dietary protein restriction or ACE inhibitor therapy can induce a similar glomerular hemodynamic effect, Paller and Hostetter[72] have suggested that reduced dietary protein alters renal hemodynamics by lowering intrarenal renin generation and angiotensin II levels.

Interrelationship of Renal Autacoids in Regulating Glomerular Hemodynamics

Inasmuch as renal hyperfiltration results from reduced arteriolar vascular resistance and an increased renal plasma flow, it would be difficult to ascribe the hemodynamic profile in states of glomerular hyperfiltration solely to a primary alteration in the glomerular action of angiotensin II. For example, infusing angiotensin II in rats results in an increase in renal vascular resistance and a decrease in the glomerular capillary ultrafiltration coefficient, with a resultant decrease in the glomerular capillary plasma flow rate and the single-nephron GFR.[82] Because hyperfiltration is associated with an increase in glomerular capillary plasma flow rate and the single-nephron GFR, a renal vasodilator must be present. Based on the studies presented, we suggest that the glomerular vasodilatation and hyperfiltration induced by diabetes mellitus, dietary protein intake and a reduced renal mass are mediated in part by an augmented glomerular production of vasodilatory prostaglandins. Other renal vasodilators may participate in this phenomenon, including atrial natriuretic peptide (ANP). In a preliminary study by Ortola and coworkers,[83] both GFR and ANP levels were elevated in rats with moderate hyperglycemia. Further, infusing a specific ANP antiserum reversed the renal hyperfiltration. Angiotensin may contribute to this hemodynamic effect by increasing the postglomerular arteriolar tone so that, while the total renal vascular resistance is decreased, a relatively greater vasodilatation in the afferent renal arteriole could account for the increased intraglomerular pressure that is characteristic in this setting. Thus, there is probably a critical

interplay between renal eicosanoids, the renin-angiotensin system and perhaps other humoral mediators in modulating glomerular hyperfiltration and hypertension. This interaction can be predicted to be complex because, on the one hand, angiotensin II stimulates prostaglandin production by whole glomeruli[37,38] and cultured mesangial cells and, on the other, renin secretion and the subsequent angiotensin II production are in part mediated by prostaglandins.[84,85]

In summary, glomerular hypertension and hyperfiltration appear to be the major pathogenic factors in the progression of renal insufficiency in several models of experimental renal disease and are modified by the quantity of protein in the diet. The altered renal hemodynamics that occur in humans with diabetes mellitus, in experimental models of renal disease in rats and in response to protein loading have a common dependency on both renal eicosanoid biosynthesis and the renin-angiotensin system. These and other autacoid systems may be a final common pathway through which these hemodynamic changes are mediated. Thus, perturbations of these vasoactive glomerular autacoids may be responsible for both renal disease and dietary protein-induced hemodynamic abnormalities that lead to progressive renal dysfunction in clinical and experimental kidney diseases.

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Epitomes
Important Advances in Clinical Medicine

Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in dermatology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Removing Tattoos

TATTOOS ARE ACCIDENTAL OR INTENTIONAL INJECTIONS of pigment into the skin. This pigment is long-lasting and, when removal is required, physicians must choose among a variety of methods, none of which will restore the skin to its pretattoo appearance.

Methods of tattoo removal include excision with primary closure or skin grafting, serial excision, tissue expansion and excision, liquid nitrogen cryotherapy, laser vaporization, dermabrasion or salabrasion, caustics, infrared coagulator and serial tangential excision. An excellent summary of tattooing and the older methods of tattoo removal appeared in a special issue on tattoos in *The Journal of Dermatologic Surgery and Oncology* in 1979.

Excision is clearly the best way to remove a tattoo that is small or configured favorably for simple primary closure. In such cases, 100% tattoo removal is assured. The procedure is simple and cost-effective and results in a predictable and usually cosmetically acceptable scar. Negative aspects of excision include a delayed widening of the scar line, hypertrophic or keloidal scarring and limited use of the affected body area until the wound gains sufficient tensile strength not to dehisce. Over joints or skin with limited suppleness, primary closure may not be possible.

When skin grafting, tissue expansion or serial excision is necessary, strong consideration should be given to alternative methods of removal. These techniques are very time-consuming and expensive, especially if time lost from work is considered. Donor scars from skin grafts add to the discomfort and cosmetic liability of the technique. Graft texture and color differences from surrounding skin may also be a problem.

Dermabrasion can be a valuable method of removing larger tattoos in areas such as the dorsal forearms where hypertrophic scars are less frequent. It is particularly helpful in removing pastel tattoos, but is poor at removing black ink tattoos. Hypertrophic scarring is a frequent complication of dermabrasion. Residual pigment shadowing frequently follows dermabrasion, and the technique does not permit total tattoo removal at the time of the surgical procedure; the surgeon does not know the result of the procedure until weeks to months postoperatively. A test area before treatment is recommended.

Laser removal of tattoos has recently gained in popularity. The versatile carbon dioxide laser is usually the laser of choice for removing tattoos. It is simple to use, compact, mobile and increasingly less expensive. The laser can generally be plugged into any office outlet. Clear glasses block the CO_2 laser light so there is excellent visualization of the operative site. With a continuous-mode operation, large tattoos can be removed quickly. The CO_2 laser is not color-specific. When correctly used there should be little thermal damage of adjacent tissues. A tattoo can be completely removed in one session, and there is no bleeding of the surgical site. Healing occurs by secondary intention, and the patient can return to work immediately after the operation. This alone makes laser surgery cost-effective. The laser treatment can be extended to adjacent areas to avoid a "negative image" scar. Postoperative care is simple and there is little or no postoperative pain. Areas previously thought difficult to treat such as the ankles and backs of the fingers may be treated with a CO_2 laser.

Test areas generally should be done before laser tattoo removal. Occasionally a "blush of dye" may remain at the operative site. Hypertrophic scars can occur, and thumb-web tattoos are especially prone to excessive scarring. Pastel colors are not as preferentially removed by laser as they are by dermabrasion. Old tattoos are difficult to remove and often leave a blush of pigment in the scar. There is a "cigarette paper" texture to the healed skin, and the skin remains susceptible to trauma for as long as a year after a laser procedure. Some deep tattoos cannot be removed by laser vaporization. Tattoo dots ("crazy dots") are not well removed by laser but are easily removed by punch excision. Skin color changes frequently occur after a laser operation, but these usually return to near normal within two years. Homemade tattoos are usually not more difficult to treat than professional tattoos.

No method can remove a tattoo without a scar, and patients must be aware of the complications of the tattoo removal method that is used.

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Lyme Disease

LYME DISEASE, which is caused by a tick bite, initially presents with erythema chronicum migrans, fever and arthralgias. The rash spreads out from the bite, forming a raised border as it clears in the middle. Neurologic signs may develop later that can mimic viral meningitis or Bell's palsy and cardiac problems including myocarditis. The disease was first described by Steere in Lyme, Connecticut. In the West, the deer tick *Ixodes pacificus* transmits the disease. A history of an outing to a wooded area is common. The causative organism disseminated by the tick is the spirochete *Borrelia burgdorferi*.

The diagnosis can be confirmed by identifying antibodies to the *Borrelia* organism with either an immunofluorescence test or an enzyme-linked immunosorbent assay (ELISA). The fluorescent treponemal antibody absorption test may be positive in these patients. False-positive results, particularly with immunofluorescent testing, may be caused by other *Borrelia* spirochete infections, syphilis or possibly connective tissue disease. Apparent differences reported between immunofluorescent and ELISA testing for the *Borrelia* antibody is a major problem impeding advances in this area.

Antibiotic treatment with tetracycline or penicillin is usually curative for diseases caused by *B burgdorferi*.

Acrodermatitis chronica atrophicans, a cutaneous disease with both sclerotic and atrophic features, is also caused by *B burgdorferi*.

Other dermatologic diseases in which *B burgdorferi* has been suggested as a cause include localized scleroderma, lichen sclerosus et atrophicus and lymphadenosis benigna cutis. Preliminary serologic studies and possible identification of the organisms in affected tissues have been reported in these conditions but need further clarification.

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Ketoconazole Use in Tinea Versicolor

IN TWO STUDIES involving 62 patients, the use of ketoconazole, 400 mg in a single dose, was effective in clearing tinea versicolor, both clinically and mycologically, in 60 of the patients treated. The drug should be taken with breakfast, preferably with fruit juice. Because ketoconazole is rapidly excreted in sweat, patients should not bathe for 12 hours after taking the drug. If a patient is also taking cimetidine or β-blocker drugs, these must be withheld until two hours after taking the ketoconazole. If a patient is achlorhydric, the drug can be taken with lemon juice or a pharmacist can mix the two tablets (equivalent to 400 mg of ketoconazole) with an 8-ml aqueous solution of 0.2N hydrochloric acid. Caution the patient to take the mixture through a straw and immediately drink water to prevent damage to the teeth. Liver function tests are not indicated as hepatotoxicity is rare (1/15,000) and has never been reported in short-term therapy. Patients treated with this regimen have not noted any side effects. Residual hypopigmentation from the fungus may persist, however, until the patient is exposed to ultraviolet light.

Ketoconazole may enhance the anticoagulant effect of coumarin-like drugs. The use of ketoconazole with rifampin, isoniazid, phenytoin and hypoglycemic agents is not recommended, nor should ketoconazole be given to pregnant or nursing women who have tinea versicolor.

Preliminary studies indicate that recurrences are less frequent than those following topical therapy. Patients prefer the ketoconazole regimen, if the disease recurs, rather than other forms of treatment.

In summary, a single 400-mg dose of ketoconazole will clear tinea versicolor, provided that the patient complies with the regimen.

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Rausch LJ, Jacobs PH: Tinea versicolor: Treatment and prophylaxis with monthly administration of ketoconazole. Cutis 1984 Nov; 34:470-471

Recent Advances in Clinical Use of Retinoids

VITAMIN A WAS FIRST USED about 40 years ago as therapy for various skin diseases and is a well-known regulator of epithelial growth and differentiation. Retinol taken in high oral dosages can cause significant toxicity problems, such as fatigue, headaches, cheilitis, anorexia, peeling of the skin, pseudotumor cerebri, papillary edema, hepatotoxicity, skeletal hyperostosis and lipid abnormalities. Because of this toxicity the use of vitamin A declined, but in the 1970s several vitamin A analogs were investigated as treatment of diseases such as acne, psoriasis, ichthyosis and other disorders of cornification. The beneficial effects of the use of 13-*cis*-retinoic acid for the treatment of lamellar ichthyosis were described in 1976 and shortly thereafter in patients suffering from severe nodular cystic acne. In subsequent studies, 13-*cis*-retinoic acid was found to be of value in generalized pustular psoriasis but was much less effective for other forms of psoriasis vulgaris. Etretinate was reported to have significant effects as therapy for severe forms of psoriasis vulgaris and was approved by the Food and Drug Administration in late 1986 as a treatment of severe recalcitrant psoriasis, exfoliative erythrodermic psoriasis and generalized pustular psoriasis. Its optimal use in severe plaque psoriasis is in combination with other forms of therapy, such as psoralen and high-intensity ultraviolet A phototherapy. Etretinate and 13-*cis*-retinoic acid have all the side effects listed above with retinol.

One additional problem of toxicity with etretinate is that it continues to be excreted for a long period after the drug therapy has been stopped. In women of child-bearing age, therefore, this drug should not be used, as the risks of teratogenicity may still be present for as long as two years or more after its use has been discontinued.

Clinical studies are currently being undertaken with the carboxylic acid derivative of etretinate, which will be known in the United States as acitretin. This drug has the efficacy and toxicity of etretinate but is much more rapidly excreted and therefore could be given to women of child-bearing age pro-

viding contraception is used during the drug therapy and for four weeks thereafter. The hope is that newer retinoids will be discovered that may have less toxicity but retain clinical efficacy. Systemic retinoids are valuable drugs that need to be used cautiously by dermatologists skilled in their use. They represent a major advance in the management of patients with severe selected dermatoses.

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Liposuction in Dermatology

IN THE AMAZINGLY SHORT TIME since liposuction was first introduced to cosmetic surgeons in the United States, it has been standardized and vastly improved. American ingenuity and manufacturing preeminence have produced many new and better suction pumps and cannulas. Today a properly selected patient can safely have a liposuction operation under local anesthesia on an outpatient basis, although for patients requiring large amounts of fat removed, general anesthesia may be preferred.

Most office-based surgeons use a variation of the wet technique. A hypotonic saline solution, hyaluronidase, epinephrine and lidocaine are injected into the area to be suctioned. This provides adequate anesthesia, and the dilute epinephrine reduces the bleeding. The use of the wet technique seems to reduce or totally eliminate the problems with fluid balance and blood loss. It is not uncommon to stand a patient up during the procedure so that the gluteal crease and the lateral thighs can be accurately sculptured.

Narrower cannulas are generally used today: 4- and 6-mm cannulas for the trunk and proximal extremities and 3- and 4-mm cannulas for the submental and jowl areas. There are several new designs for the tips of the instruments, including a spatula-shaped tip, multiple ventral openings and partial frontal openings. All of these changes have made the operation physically easier for physicians and far less traumatic for patients.

As is true with most new techniques, the success rate goes up and the complication rate goes down as physicians become more knowledgeable in selecting patients. Nowadays, very gratifying results are consistently produced on the lower abdomen, the lateral thighs and the medial knees. Good results are commonly achieved on the upper abdomen, the medial thighs and the ankles. The "love handle" area requires more experience and judgment because often it is a fold of heavy skin rather than excess fat. Also, the results after suction of that area may take as long as 12 months before the full benefit is achieved.

Liposuction can be used alone or in conjunction with a face-lift procedure for the submental and jowl areas. Many surgeons use liposuction as an adjunct to the face-lift procedure, both to improve the results and also as a technical aid to cleaning fat from the platysma muscle or undermining the cheek flap.

Some giant lipomas can be treated with liposuction. Male gynecomastia will respond to such treatment. Occasionally the lateral and medial arms have a fat collection that is successfully treated by liposuction.

The major complications include fluid loss, blood loss, infection and hematoma. Some of these complications have been catastrophic, with infections leading to disseminated intravascular coagulation, and there are reports of deaths due to pulmonary emboli. There are also reports of visceral perforation. As tragic as these events are, the incidence is low and the causes are presumed to be associated with poor surgical judgment, poor follow-up, inadequate fluid replacement or inadequate attention to sterility. Almost all of these major complications have occurred in patients who were treated in a hospital general surgery or come-and-go surgery. The experience to date thus does not support the contention of those malpractice insurance carriers who want to limit their coverage to only those physicians with hospital privileges for liposuction operations.

Minor complications include irregular or wavy skin. Most of the time this will soften in 6 to 12 months. Numbness is one of the most common complications, but its incidence does not exceed 5% of patients. The frequency of all of these complications is acceptably low in exchange for the gratifying results in an area where previous techniques were woefully inadequate.

Liposuction has made us aware that body fat differs genetically. Some areas are slow to catabolize by ordinary diet restriction. Studies are under way to examine the metabolic variation of localized fat collections and to assess the overall effect on metabolism when selected amounts of fat are removed.

This procedure is appropriately gaining popularity as the medical profession is better able to select and deliver satisfactory results in a safe setting. Many persons with figure fault deformities have had to deal with the social consequences. Before liposuction procedures, such persons had to live in a semistarved state, and even that was not always helpful.

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Using Lasers in Skin Surgery

LASER IS AN ACRONYM for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation. The basic principle of lasers is that a high-intensity monochromatic collimated beam is directed to target tissue and produces localized tissue injury.

The most commonly used apparatus today is the carbon dioxide laser, which emits a beam in the far infrared portion of the light spectrum. This laser light is absorbed by water and produces localized tissue vaporization or coagulation as the tissue is rapidly heated. The other frequently used laser is the argon laser, which produces a blue-green light in the visible spectrum that is selectively absorbed by hemoglobin and results in coagulation.

The CO_2 laser has a wide variety of uses in dermatology, including vaporizing benign cutaneous neoplasms and warts, excising skin cancers, removing superficial pigmented lesions such as lentigines or seborrheic keratoses, removing tattoos and excising vascular proliferations such as port-wine stains

or cavernous hemangiomas. The argon laser is mainly used to ablate vascular malformations and vascular tumors, but is also used to treat some benign pigmented lesions, warts, benign tumors and tattoos.

Laser ablation of abnormal tissue does not differ qualitatively from other modes of tissue destruction. There are, however, a number of important advantages to this mode of treatment. Extreme localization of the beam minimizes perilesional injury. The laser is excellent at cauterizing small blood vessels so that a dry operative field and reduced postoperative edema are obtained. The wound is sterilized by the laser beam and, thus, one may operate in a contaminated field. In addition, postoperative pain is often less than with other destructive procedures because small nerve endings are sealed.

There are several disadvantages to laser surgical procedures. The equipment is expensive and not highly portable. In addition, it is technically sophisticated and, thus, may be prone to major malfunctions. Because the beam is so powerful, human error in its use can lead to significant cutaneous burns or eye injuries.

The near future should bring greater use of a newly developed tunable dye laser that uses a carefully chosen wavelength (577 nm), which is very selectively absorbed by blood. Thus, abnormal vascular channels can be ablated without damaging surrounding normal structures.

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Dysplastic Nevi—Markers and Precursors of Malignant Melanoma

THE INCIDENCE of malignant melanoma is doubling every decade and will affect 25,800 Americans this year, of whom 5,800 will die. No effective treatment is currently available for those with metastatic disease, the only cure for melanoma being early detection and prompt surgical excision.

More than half of those in whom melanoma develops are marked by a recently discovered, clinically distinctive type of nevus that shows histologic dysplasia. "Dysplastic" nevi often appear during adolescence, giving alert clinicians time to spot affected persons and to train them in self-examination and periodic professional examinations in time to intercept developing melanomas during the highly curable, superficial radial growth phase. Inheritance is autosomal dominant with a high degree of penetrance but with a great variety of phenotypic expression, varying from more than 50 large, irregularly pigmented lesions in more severely affected cases to the more common presentation of several or even solitary small, subtle lesions within the same family. Unlike common nevi, dysplastic nevi may continue to appear lifelong, past young adult years.

Any "new" or changing nevus occurring after age 30 should be carefully examined for evidence of melanoma or dysplasia. Identification requires bright, close, tangential, incandescent illumination (preferably halogen) within 30 cm (12 in) of the skin with an examination lamp. Gently stretching the skin unfolds the skin creases, revealing early signs of border irregularity or suffusion of pigment into surrounding skin, speckled or irregular patterns of brown, black or faint pink and sometimes a relatively lighter pigment in those creases. Most dysplastic nevi have at least a small ring of flat pigment surrounding them, and many are only minimally elevated. Confirmation requires histologic examination, preferably of two or three of the most suspicious lesions. In patients with the dysplastic nevus syndrome, about a third of melanomas arise from the dysplastic nevi themselves, a third from normal-appearing nevi and a third apparently de novo from the surrounding skin.

In families with several members affected with dysplastic nevi and with a history of multiple melanomas, an affected person's risk of melanoma developing by age 59 may be 56%. As much as 7% of the white population in the United States may be affected with dysplastic nevi but are without a family history of multiple melanomas. The lifetime risk of melanoma in these persons is under investigation and has been estimated at 6%, high enough to warrant monthly self-examinations, periodic professional complete skin examinations and precautionary sun-exposure and sunburn-reducing techniques. Family screening of their relatives by the author in a collaborative study with the National Cancer Institute has detected some previously undiagnosed melanomas.

For color photographic resources, write to:

- The Skin Cancer Foundation, 245 Fifth Ave, New York, NY 10016.
- The Atypical Mole and Melanoma Education Foundation, PO Box 2099, Napa, CA 94558.
- Norcal Mutual Insurance Company, Loss Prevention Dept, 333 Market St, San Francisco, CA 94105 (videotape entitled "Melanoma: A costly oversight.")

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Contraindications for Using Topical Steroids

IN PRESCRIBING the topical use of steroids, physicians must be aware that there are certain conditions when topical steroids are relatively or absolutely contraindicated. They must also be alert to the fact that any steroid, and in particular potent and superpotent agents, may in themselves cause topical and systemic side effects.

Using topical steroids to treat primary bacterial infections is not only *absolutely contraindicated,* but the steroid may mask the bacterial infection by its vasoconstrictive and anti-inflammatory properties, making diagnosis and treatment even more difficult. Impetigo, furuncles and carbuncles, paronychia, ecthyma, erysipelas, cellulitis, lymphangitis and erythrasma are all conditions in which the use of topical steroids is to be avoided.

Some eczematous dermatoses, blistering eruptions and papular urticaria due to bites—such as scabies—may become secondarily infected. These macerated, inflamed lesions may be treated with topical steroids in conjunction with an appro-

priate anti-infective agent. While topical steroids may help to reduce pruritus and inflammation, they should never be the first line of therapy directed at the infection itself.

Relative contraindications include *Candida* and dermatophytes—because these organisms grow well on macerated skin, the use of a topical steroid in conjunction with an appropriate anti-infection agent may occasionally be appropriate; herpes simplex and zoster—customary treatment must be directed at the virus itself, but some physicians use a mild- to mid-strength topical steroid to reduce the burning and itching of these disorders and even intralesional steroids in an attempt to reduce the risk of postherpetic neuralgia in patients with zoster. Extreme caution must be used when topical steroids are applied to the face.

Potent and superpotent agents—betamethasone dipropionate (Diprolene), clobetasol propionate (Temovate) and diflorasone diacetate (Psorcon)—have a higher propensity to cause topical side effects such as atrophy, stria, purpura or even ulceration, particularly when used in thin-skin areas (periorbital and groin regions), under occlusion or in a pediatric patient. Acnelike eruptions—rosacea, perioral dermatitis—may occur on the face with virtually any topical steroid. Glaucoma has been implicated in many topical agents used around the eyes.

Practitioners must be aware that package inserts for some superpotent agents warn against the use of occlusion or in pediatric patients and require a "rest" period after two weeks of use to reduce the risks of topical and systemic side effects, especially adrenal suppression.

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Bowenoid Papulosis

BOWENOID PAPULOSIS is a unique and distinctive neoplasm of the genitoanal region recently shown to be virally induced. Known by this name and several others over the past 30 years, the condition has been unified by histopathologic changes similar to squamous cell carcinoma in situ (Bowen's disease).

Bowenoid papulosis primarily affects sexually active young adults and appears clinically as multiple skin-colored or pigmented papules on a circumcised penile shaft or labia majora and minora, but it may occur anywhere in the genitoanal region. The papules may be discrete, grouped, linear, confluent, smooth or verrucous in morphologic appearance and texture. They are usually asymptomatic but occasionally itch. Macular and leukoplakia-like lesions have been described.

The differential diagnosis includes warts, condyloma acuminatum, seborrheic keratoses, nevi, lichen planus and other papular conditions. Generally the larger red patches and plaques of Bowen's disease and erythroplasia of Queyrat are not confused with bowenoid papulosis.

On histopathologic examination, however, bowenoid papulosis bears a remarkable similarity to the atypia of Bowen's disease, with only minimal differentiating features. Because of this potential confusion and unawareness of the existence of bowenoid papulosis, unnecessary ablative procedures have been done in the past.

The natural history of this condition ranges from spontaneous regression over a period of months to rarely evolving into invasive squamous cell carcinoma. Without treatment, most remain benign and unchanged.

Prior suspicions of a viral cause have been confirmed by the identification of human papillomavirus (HPV) type 16. Other recent studies have linked bowenoid papulosis with HPV 16-induced cervical dysplasia and neoplasia. There is growing evidence that this disease is sexually transmitted, thus raising many new concerns regarding an otherwise benign process.

Therapeutic modalities that have been advocated include topical application of retinoic acid or 5-fluorouracil, cryotherapy, electrodesiccation with or without curettage, shave biopsy, surgical excision, vaporization by laser and interferon injection. Clinicians should use selective judgment in choosing an appropriate conservative modality, as some cases spontaneously regress and malignant degeneration is rare. Because recurrence of bowenoid papulosis is frequent, a biopsy should be taken of lesions recalcitrant to standard therapy to exclude malignancy.

In view of assumed sexual transmission and a proven association with cervical neoplasia, our emphasis should be on prevention. A patient with bowenoid papulosis should be thoroughly educated regarding HPV infections and the use of condoms (or abstinence) strongly advocated. Patients should be routinely examined for recurrence. Female patients or sexual partners of male patients with this disorder should be followed with regular cytologic, colposcopic and histologic examinations.

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Cutaneous Manifestations of the Acquired Immunodeficiency Syndrome (AIDS) and AIDS-Related Conditions

INFECTION BY THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) and subsequent depletion of immune function may involve a variety of organs in the acquired immunodeficiency syndrome (AIDS) and AIDS-related conditions (ARC). The skin as a mirror of internal disease provides a readily accessible diagnosis of AIDS or ARC in many cases.

Viral and fungal infections of unusual severity were recognized early on as harbingers of AIDS or ARC. Other infectious agents occurring as unusual skin lesions have been reported recently. Herpes simplex virus, *Cryptococcus neoformans, Histoplasma capsulatum* and *Mycobacterium avium-intracellulare* may appear as skin ulcers, vesicles or granulomas. Herpes simplex virus in particular may cause severe, chronic perirectal ulcerations and abscesses. Mucosal infections with *Candida albicans* usually present as white patches in the buccal and oropharyngeal areas. Hairy leukoplakia—white roughened areas along the sides of the tongue—has recently been linked with the Epstein-Barr virus and occasionally *Candida*, herpes and human papillomavirus.

Florid presentations of warts and molluscum contagiosum in a person with risk factors for HIV infection should suggest close observation and counseling.

In about 40% to 50% of patients with AIDS or ARC, a malignant process will develop during the course of the disease. An aggressive form of Kaposi's sarcoma, associated with profound lymphocytic depletion, became one of the criteria for the diagnosis of AIDS in the early 1980s. Vigorous treatment of Kaposi's sarcoma has resulted in worsening of the patient's overall condition in many cases. Other malignant disorders include squamous cell carcinoma, especially of the perirectal area, and lymphomas of both the Hodgkin's and undifferentiated varieties. Treatment of these conditions is usually of some benefit.

Common skin conditions that may be recalcitrant to conventional therapy when associated with AIDS or ARC include psoriasis and seborrheic dermatitis.

It is estimated that between 1 million and 1.5 million persons in the United States are infected with HIV (Centers for Disease Control, Atlanta). In a person with risk factors for HIV infection, examination of skin and mucous membranes may yield an early diagnosis of AIDS or ARC.

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Short-Contact Anthralin Therapy for Psoriasis

ANTHRALIN WAS FIRST USED in the 1920s as a treatment of psoriasis vulgaris. Over the years, it has been shown to be one of the most effective topical treatments of stable psoriasis. No systemic toxicity has been reported. Its side effects, however, of staining the skin and everything with which it comes in contact, as well as irritating uninvolved skin, have limited its use. Efficacy and side effects are both dose-related and may be difficult to separate. Many schedules have been devised to maximize efficacy and patient compliance while reducing side effects; until recently, however, anthralin use was practically impossible in an outpatient population.

In 1980 the concept of short-contact therapy with anthralin was developed. Basically, this involves applying higher concentrations of anthralin to suitable psoriatic plaques for shorter periods of time than with traditional several-hours or overnight treatment with an anthralin hard paste. After an appropriate period, the anthralin is removed. The basis for this treatment lies in pharmacokinetic studies that show that anthralin penetrates faster through involved psoriatic epidermis than through uninvolved epidermis. At the time of removal, penetration has occurred mainly in the diseased skin. Controlled studies have shown that short-contact therapy is effective in clearing psoriasis.

Various short-contact regimens have been used. Patient compliance is optimal when periods of application from 20 to 60 minutes are used. This therapy also requires an intelligent and motivated patient because side effects are not infrequent. Stable plaque-type psoriasis is the preferred indication for this regimen. Anthralin concentrations from 0.1% to 2.0% have been used in a variety of vehicles. Creams and ointments provide greater patient compliance than hard paste; newer formulations are being developed. The initial contact time should be from 15 to 20 minutes, then the anthralin should be thoroughly removed with a solvent suitable for the base (soap or petrolatum) and an emollient applied to the skin. Therapy should be interrupted if persistent irritation occurs or if psoriasis is rapidly spreading. Topical steroids may be used to treat anthralin irritation.

The combination of short-contact anthralin therapy with other psoriatic treatment modalities, such as ultraviolet A or B light, tar, retinoids, topical steroids and psoralen plus ultraviolet A light, may improve the therapeutic response. Further studies are being conducted with such combinations in attempts to achieve maximum psoriatic clearing in an outpatient setting.

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Editorials

Light at the End of the Tunnel?

In an address before a recent meeting of the American Bar Association in San Francisco, Lee Iacocca, Chairman of the Chrysler Corporation, is reported (*San Francisco Chronicle*, Aug 11, 1987, p1,22) to have referred to litigious lawyers as "Public Enemy No. One," and he then went on to say that the number of product liability suits rose 1,000% during the period 1975 to 1985 and the amount of jury awards doubled during this time. He was further reported as stating that although cars get safer every day, automobiles account for half of all the injury suits filed and half of the awards, and that Americans are spending $30 billion a year suing each other and thus creating a climate that discourages risk taking in business, which is all important to success and even survival in a competitive world. He noted that "other countries don't spend their time looking for Mr. Deep Pockets" and called attention to the number of lawyers we have in this country by suggesting that "Japan has about as many lawyers as we have sumo wrestlers."

In medicine it is professional liability more than product liability that is the problem, but the parallels are obvious enough, and many physicians would agree that a litigious public, aided and abetted by litigious lawyers, is indeed "Public Enemy No. One," and that lawsuits and the threat of lawsuits seriously interfere with professional judgment and the taking of reasonable risks that are just as essential in patient care as they are in a competitive business such as automobile manufacturing. In both, the current epidemic of litigation has a paralyzing effect on the day to day conduct of practice or business that is not in the ultimate interest of either patients or the public. And this is not to mention the costs in dollars and human resources when these are spent in expensive, time-consuming legal confrontations that only add costly heat and friction to economic systems already under strain, again whether it be automobile manufacturing or patient care. It is all too sad, but all too true, that the most certain beneficiaries of this wave of human litigiousness are the lawyers who feed, and often feed quite handsomely, off it, as Mr Iacocca pointed out in his reported speech at the American Bar Association meeting.

For quite some time physicians and their patients have been feeling the heat and friction and, in the final analysis, bearing the costs of what has surely become excessive litigiousness in health care. As an inevitable consequence, physicians and lawyers are finding themselves in open confrontation with one another, whether in the courts or in legislative arenas, and it is worth noting that these confrontations are always on the lawyers' turf and are always conducted under rules of the game that are basically determined by lawyers.

Perhaps one can take heart, however. There may be a reason for hope. When someone of Lee Iacocca's prestige and stature in the business and industrial world calls the spade of excessive litigation the spade that it is, a new force of responsible public opinion has come upon the scene. With other nonprofessional leaders of similar prestige and stature now coming forth and speaking out in like fashion, it is just possible that we are beginning to see some light at the end of what has seemed to many physicians and many nonphysicians a very long and dismally dark tunnel.

MSMW

The Geneticist's Grail

In a lecture delivered at the Western Association of Physicians meeting in Carmel, California, on February 3, 1987, Dr Ray White and co-workers reviewed and updated the current strategies used in the identification of human genetic loci. They described the recent successes in identifying the disease loci for chronic granulomatous disease, Duchenne muscular dystrophy, cystic fibrosis and retinoblastoma and referred to impending breakthroughs in a number of other diseases such as familial polyposis, ataxia telangiectasia, neurofibromatosis and other muscular dystrophies and neurologic disorders. The localization of a disease-associated gene to a region of the genome is an important first step. Once achieved, a variety of clinical applications and potential benefits can be derived from this information.

Central to the ability to map genes to a particular locus was the advent of recombinant DNA technology, which has enabled investigators to isolate genes. There are two fundamental approaches to gene isolation, depending on whether or not the protein encoded by the gene affected in a particular genetic disorder is known. When the protein has been defined, the strategy for isolating the gene is now quite straightforward. It involves the use of synthetic DNA probes constructed according to the amino acid sequence or antibodies directed against the protein of interest. The probe or antibody is then used to identify the gene that codes for the recognized protein.

A more difficult task confronts investigators who are searching for genetic loci in diseases in which the affected protein is not known and the locus on the human chromosome may or may not be defined. Linkage analysis has enabled scientists recently to map and identify DNA sequences associated with this category of disorders. Successes have included some of the most important genetic conditions that, until now, had proved largely undecipherable by classical analysis—such as neurofibromatosis, cystic fibrosis, Huntington's chorea and Duchenne muscular dystrophy. The strategy for locating these genes depends on the use of DNA polymorphisms. Within the human genome are frequent variations or polymorphisms in DNA sequences, many of which are neutral. A variety of different polymorphisms exists. One type is caused by a single nucleotide change in the DNA that either creates a restriction endonuclease cleavage site or abolishes an existing one. Digesting DNA from different persons with the appropriate enzyme generates fragments of two discrete lengths according to the presence or absence of a restriction site.

Another type of DNA fragment length variation is due to tandem repeats of short nucleotide sequences that occur in many regions throughout the human genome. The function of these tandem repeats is not known, but the number of repeats in a region differs from person to person. Therefore, digesting DNA with the appropriate enzyme generates polymorphic fragments of different lengths due to the differing number of repeats. Because of the large number of variations possible in the number of repeat sequences present, instead of a two-allele system, a highly informative multiallele system results.[1,2] Each parental chromosome can then be distinguished and used to trace the inheritance of the particular segment of the genome.

The hybridization probes used to show DNA polymorphisms can be a cloned structural gene or random unique-sequence DNA fragments isolated from a human genome. Some of the tandem repeats could also be used as probes to generate multiple alleles on multiple chromosomes.[3] The general strategy for searching for disease loci when the protein is not known is to use a series of these probes and determine which segregate together with the inheritance of a disease in a family. Once such a linked DNA marker is found, it can be assigned to a specific chromosome by hybridization analysis. The disease loci of Huntington's chorea and cystic fibrosis, for example, have been localized in this manner.

The clinical application of identifying the disease loci has been rapid. Both prenatal and presymptomatic diagnostic use of these polymorphisms is beginning to have a major impact on the practice of clinical medicine. With a DNA marker close but not right at a disease locus, how does one actually find the locus itself? This involves "walking the chromosome," that is, isolating fragments of DNA adjacent to the probe until the gene itself is reached. But how does one know which piece of DNA contains the disease locus? Several strategies are available. If the disease is caused by gene deletion, finding a DNA fragment that is deleted in the disease state indicates that one is at or very close to the disease locus. A second method is to use the adjacent DNA fragments to detect abnormal messenger RNA transcripts in the disease state. A third approach involves locating functional genes in isolated DNA. The cytosine residue of CG base pairs tends to be heavily methylated in nonfunctional DNA and remains unmethylated in functional DNA. Thus, by using restriction enzymes that can distinguish methylated from nonmethylated CG sequences, it is possible to locate DNA fragments that may contain functional genes.[4] Another characteristic of nonfunctional DNA is that the sequences tend to diverge across species, while the sequences of functional genes are usually conserved. Searching for conserved DNA sequences in DNA isolated by "walking" may also indicate the presence of functional genes. The list of disease genes that have been identified this way is small but growing.

What benefits can be derived from identifying the genetic locus for a disease? First, it provides a wealth of information about how genes function and enables us to define many mutations that may give rise to disease states. For example, we have learned that more than 50 mutations may affect β-globin gene function and result in β-thalassemia. From studying how these mutations affect gene function, we have learned why fetal hemoglobin synthesis is increased in certain types of thalassemia and why some thalassemias are more severe than others.

Apart from being intellectually satisfying, a practical application of the fundamental knowledge is better diagnostic capabilities. Whereas carrier identification of diseases such as cystic fibrosis was previously difficult, and in many cases impossible, the availability of DNA probes has overcome the obstacles. Prenatal diagnosis of many genetic conditions has become possible through the use of DNA probes. By knowing the precise mutation responsible for a disease, we are now able to design specific methods to diagnose the condition in utero. As more mutations continue to be discovered, the methods for detecting them also improve. The emergence of rapid nonradioactive techniques may help to make the DNA analysis a routine procedure.

One of the most challenging problems that DNA probes may help solve in the future relates to diseases such as heart disease and cancer that are caused by the interplay of multigenic factors. Locating these genes may help to identify factors that predispose a person to these diseases and provide methods to prevent them.

The approach we have outlined is called reverse genetics. It begins with linkage analysis to determine the disease loci, followed by determination of the gene sequence and an understanding of how the gene results in the phenotypic features of the condition. Even more important than the improved diagnostic capabilities is the potential for developing the means of treating these conditions. With this goal in mind, the isolation of genes affected in genetic disorders has already stimulated intense research efforts in replacing defective genes with normal ones. Experiments are in progress to introduce cloned genes into cells to produce missing enzymes in some enzyme deficiency states.[5] Specific recombination methods to replace a diseased gene with a normal gene have also been attempted.[6] Although these approaches are highly experimental at present, some of these therapeutic modalities may become feasible in the future.

To date, the greatest impact of modern molecular biology on the practice of clinical medicine has occurred in the field of medical genetics. An ever-increasing number of single gene disorders are now amenable to diagnosis through linkage or direct analysis of the diseased gene. Strategies using linkage analysis have led to the identification of the diseased gene in several conditions that have long baffled medical researchers. The future for diagnosing most single gene disorders through DNA analysis seems very bright, and the potential exists for effective treatment for some of them.

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Nutrition During the Continuum of Development

IN THEIR REVIEW in this issue, Kennaugh and Hay summarize information about the provision of nutrients to mammalian fetuses and the nutritional requirements of newborn human infants. By placing these respective summaries in sequence, they highlight the developmental changes in nutrient provision that occur at birth. Concurrently with the replacement of the placenta by the gut as the route for nutrient delivery and the substitution of human milk for maternal plasma as the source, both qualitative and quantitative changes in nutrition occur.

Before birth, the fetus is provided carbohydrate as glucose

and lactate; after birth the carbohydrate supplied by human milk is predominantly lactose, a disaccharide of glucose and galactose. Galactose thus replaces lactate in the dietary mix of carbohydrates. The mammalian fetus is provided relatively little fat by the umbilical circulation, while after parturition, the human mammary secretions provide an infant diet that is rich in fats. During the period of very rapid intrauterine growth, the fetus is provided with an apparent excess of amino acids relative to tissue accretion needs, and the total amino acid concentration in fetal plasma exceeds that in the maternal plasma, whereas after birth the intake of various proteins provided by human milk may be growth-limiting to a low-birth-weight human newborn.

Certain of these developmental changes in macronutrient provision have plausible explanations, even if they are not completely understood. For example, the relative impermeability to lipids of the placentas of some species—sheep, for example—explains the scant lipid content of the fetal diet, but the advantages or disadvantages to a fetus of a placenta that is relatively impermeable to lipids are unclear. Active transport of amino acids by the trophoblast is the mechanism by which a fetus acquires most nitrogen and by which amino acids may be transferred from a lower concentration in maternal plasma to a higher concentration in fetal plasma, but knowledge that the active transport system operates does not inform us if the higher fetal plasma amino acid concentrations are essential to sustain the rapid fetal growth rate or if the growth rate diminishes after birth as a consequence of lower plasma amino acid concentrations in infants who are fed enterally. These are questions regarding the interactions between major nutrients and development to which we have no answers; there are probably many more questions that pertain to nutrients that are provided in smaller quantities—for example, trace minerals and vitamins.

In addition to underscoring peripartum nutritional changes that occur, this review of the continuum of fetal to infant nutrition highlights our ignorance of safe, maximum nutrient provisions during development. Most of the effort of investigations of fetal nutrition has been directed toward identifying the nutrients used by a fetus, the rates of their provision to the fetus and the consequences on fetal growth or development of an insufficiency of a particular nutrient. Similarly with infant nutrition inquiry, most efforts have been to determine minimal or optimal requirements of various nutrients for term or preterm infants when the nutrients are administered either intravenously or enterally. For human infants, little is known about maximum, safe intakes of individual nutrients. The Food and Drug Administration specifies that infant formulas should provide minimum amounts of 29 nutrients, but maximum concentrations can be specified for only 9 of these.

That throughout gestation a fetus may be exquisitely sensitive to excessive nutrient supplies is becoming apparent with regard to glucose. Evidence that excessive glucose is teratogenic comes from both epidemiologic and experimental observations. Structural malformations occur more frequently in gestations complicated by maternal diabetes mellitus, and the less well-controlled the diabetes, the higher the incidence of malformation. Furthermore, a recent report suggests that glucose homeostasis in nondiabetic women is an important factor in structural malformations; the higher the two-hour plasma glucose concentration during a glucose tolerance test in nondiabetic women during the third trimester, the greater the incidence of certain malformations. These epidemiologic studies in humans have an experimental counterpart in rats. When rat embryos are grown in culture in vitro, at a critical period during gestation, an excess of glucose or certain other hexoses produces fetal malformations. Added arachidonic acid may block this teratogenic effect of hyperglycemia.

In addition to structural abnormalities, an excess of glucose provided to a fetus may also produce metabolic and cardiovascular pathophysiologic effects. For instance, in instrumented sheep near term, umbilical blood flow diminishes by as much as 40% during acute maternal hyperglycemia induced by D-glucose infusion into a ewe. Thus, glucose is emerging as a nutrient that appears to have many deleterious effects if provided to a fetus at any time during gestation in excess of a safe value.

In view of these distinctly adverse consequences of an excess glucose provision, the saturable mechanism by which glucose is transferred across the placenta may be looked upon as a protective device to prevent excessive glucose flux to a fetus during maternal hyperglycemia. In sheep the mechanism for facilitated transfer becomes saturated when the maternal blood glucose concentration is approximately two to three times the blood glucose concentration of well-fed ewes.

The toxic effects of excessive provision of some nutrients to the infant have been described, but knowledge of the safe upper limit of most nutrients is not at hand. Among those nutrients that might produce toxic effects if provided in excess of safe maximum limits are protein, fluoride and phosphorus. The route by which nutrition is provided is important in this consideration, for analogous to the saturable mechanisms for glucose transfer across the placenta, there are transfer and absorption processes in the gastrointestinal tract that may safeguard against excessive intake by an infant. When the gut is bypassed and nutrients are provided intravenously, however, upper limits that are safe for enteral provision of nutrients may need to be revised downward. Because of this concern, the separate descriptions by Kennaugh and Hay for nutrient requirements provided intravenously and enterally are important.

Kennaugh and Hay include recommendations for infant intakes of many nutrients, including calcium, phosphorus, trace minerals and vitamins; their review of knowledge of fetal provisions, however, omits discussion of many nutrients. While much less is known of the fetal provision and metabolism of these quantitatively less important nutrients, there is information regarding placental transfer of these and of their roles in fetal development. Readers might wish to refer to several of the references below for additional information.

Another aspect of nutrition during development that is presently unfolding is the interplay between the changing composition of human milk during the course of lactation and the developing function of the neonatal gastrointestinal tract. Colostrum contains growth-promoting substances that appear to play a role in the rapid growth of intestinal mucosa, which of course is needed for optimal absorption of the nutrients contained in milk. Colostrum also stimulates the synthesis and release of endogenous gastrin in suckled newborn subjects of several species, and the high levels of gastrin appear to promote the growth of gut mucosa and pancreas. During the immediate neonatal period, however, high levels of gastrin do not cause excessive gastric acid secretion. Furthermore, milk exerts a gastric protective effect on the gut mucosa, continuing after birth the protective effect of swal-

lowed amniotic fluid on the fetal gut. Finally, not only are quantities of mucosal enzymes increasing during gestation in preparation for enteral feeding, but the motility of the small intestine also increases strikingly at about 28 to 31 gestational weeks. In this latter instance, function does not appear to depend on nutrient intake but, instead, to anticipate it.

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Markers for Mono

INFECTIOUS MONONUCLEOSIS is an important disease for teenagers in that it is one of the diseases pinpointed as causing a great deal of absenteeism from school. One of the diagnostic tests I use is: are they well enough to go out on the weekends but not well enough to go to school? But the signs are characteristic as well: adenopathy, fever, pharyngitis, splenomegaly, and the characteristic skin rash that can almost be a diagnosis by putting these kids on amoxicillin and seeing the nice rash that comes out. It is not a sign of penicillin allergy.

—DONALD G. NORRIS, MD

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Case Reports

Influenza B Encephalitis

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SEROLOGICALLY CONFIRMED influenza B encephalitis has not been reported in adults. This disorder has been described for many years, with an association being inferred from a temporal relation between neurologic disorders and influenza epidemics.[1,2] Horner has presented serologic evidence of encephalitis caused by influenza A.[3] A teenaged girl has been reported to have an acute encephalitis associated with a nasopharyngeal culture positive for influenza B, but serologic testing was not reported.[4] During an influenza B outbreak in Chicago in 1971, 16 grade school students with encephalopathy (of which half had Reye's syndrome) showed serologic evidence of influenza B infection.[5] In the following report, encephalitis developed in an adult patient with a serologically documented influenza B infection.

Report of a Case

The patient, a 41-year-old man, was admitted to hospital because of confusion of 18 hours' duration. One week before admission the patient had a febrile illness with cough and rhinitis. This resolved spontaneously within three days and he returned to work for two days. On the morning of admission the patient complained of headache and was noted by his wife to be confused. This confusion progressed, prompting transport to the emergency room.

There was no previous history of neurologic problems, and the patient was not known to smoke, drink alcohol or take medication. No recent head trauma or loss of consciousness was reported.

The temperature was 38°C (100.4°F), the pulse was 100 per minute, the respirations 34 and the blood pressure was 184/90 mm of mercury. On examination the patient was disoriented and lying still. He was normocephalic and resisted neck flexion. Pupils were equal, 5 mm and briskly reactive to light, the fundi appeared normal and the eyes moved in a wandering, conjugate fashion. The tympanic membranes were gray with normal landmarks. Cardiorespiratory and abdominal examinations showed no abnormalities. The patient did not respond to verbal requests, but on tactile stimulation would withdraw appropriately and say "don't." The face was symmetric with normal corneal reflexes bilaterally. He had a normal gag reflex and moved all four extremities strongly. Deep tendon reflexes were normoactive and symmetric. Babinski's sign was absent.

A urine specimen on analysis was normal. The hematocrit was 40.9% and a leukocyte count was 9,300 per μl, with 92% neutrophils, 6% lymphocytes and 1% basophils. A serum sodium level was 137 mEq per liter, potassium 4.0 mEq per liter, urea nitrogen 15 mg per dl, glucose 235 mg per dl (after administration of a solution of 50% dextrose in water), serum aspartate aminotransferase (glutamic-oxaloacetic transaminase) 15 units per liter and blood ammonia 24 mmol per liter (normal 11 to 35). A cerebrospinal fluid (CSF) specimen was clear, with 6 leukocytes (80% lymphocytes and 20% monocytes) and 0 erythrocytes per μl. The CSF glucose level was 81 mg per dl and the protein 54 mg per dl (normal 15 to 45). A Gram's stain and india ink preparations were negative for organisms. Computed tomography revealed no abnormalities of the brain.

On the first day of admission the patient had progressive deterioration of his sensorium, a temperature elevation to 39°C (102.2°F) and a generalized tonic-clonic seizure. A regimen of phenytoin was started. By 36 hours after admission he was unresponsive to deep pain. Magnetic resonance imaging of the brain was normal. A repeat lumbar puncture showed the CSF to be clear with 21 leukocytes (77% lymphocytes, 20% monocytes and 3% neutrophils) and 1 erythrocyte per μl. A glucose level was 79 mg per dl and protein 65 mg per dl. The patient became responsive to pain on the fourth hospital day and was conversant by the eighth hospital day. He remained febrile until the fifth hospital day. He returned to work within a month of his hospital admission and has remained without neurologic sequelae.

Bacterial culture of blood, urine and CSF specimens was negative. Viral screening cultures of CSF, nasopharynx and rectal specimens were negative. Viral antibody titers (complement fixation method) were evaluated from serum specimens drawn on the day of and 18 days after admission. The titer for influenza B showed a fourfold rise, from 1:16 to 1:64. No change in titer was noted for Rous sarcoma virus, herpes simplex, mumps or influenza A.

Discussion

Many neurologic complications are linked with influenza B infection. These include Reye's syndrome, transverse myelitis, the Guillain-Barré syndrome and encephalitis.[1,2,4-6] Both acute and postinfectious influenza B encephalitides have been described, with the former being confirmed by viral culture.[4] This case represents the first serologic confirmation of influenza B encephalitis in an adult. The time course of the illness suggests a postinfectious encephalitis, which would account for the negative culture results.[7]

Influenza B is generally considered to be a mild disease in otherwise healthy adults.[8] This report documents a serious neurologic complication of influenza B infection and reemphasizes the need to monitor influenza type B antibodies in patients with wintertime encephalopathic illnesses.[5]

(Bayer WH: Influenza B encephalitis. West J Med 1987 Oct; 147:466)

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Maxillary Sinusitis—The Focus of Toxic Shock Syndrome in a Male Patient

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THE TOXIC SHOCK SYNDROME was first labeled by Todd and associates[1] in 1978, when they described the syndrome in seven children ranging in age from 8 to 17 years. In 1980 Shands and colleagues[2] positively linked the syndrome with tampon use. The syndrome's high mortality rate, coupled with its ties to a widely used product, generated substantial public interest and concern. Obscured in the subsequent media coverage was a number of cases linked with other causal agents.[3]

The toxic shock syndrome has occurred in patients undergoing deliveries or surgical procedures. Jacobson and coworkers[4] reported that nasal operations, in particular, have been associated with the syndrome, with a prevalence similar to that occurring in menstruating women.[5-8] They also noted another rare occurrence of the syndrome, categorized as "spontaneous." Reingold and associates,[9] in a review of 130 cases of nonmenstrual toxic shock, reported a variety of infection sites and noted that 10% of cases had an "uncertain cause."

The clinical definition of the toxic shock syndrome is provided by Davis and associates[10] in consultation with other noted toxic shock researchers. They described the diagnosis as requiring the presence of a high fever (>38.5°C or 102°F), hypotension or orthostatic dizziness, diffuse or palmar erythroderma with subsequent desquamation of the skin of the extremities, hyperemia of the conjunctivae or the mucous membranes of the vagina or oropharynx and multisystem dysfunction. This dysfunction must include at least four of the following: vomiting or diarrhea, alterations in consciousness, impaired renal function, thrombocytopenia, an elevated muscle creatine kinase level, cardiopulmonary dysfunction and decreased serum calcium and phosphate levels. Laboratory studies must eliminate all other causes to confirm the diagnosis.

An atypical case that meets the clinical definition of the toxic shock syndrome occurred in Salt Lake City near the end of 1984. A 27-year-old male hydrologist went to a family practice clinic complaining of a "bad case of the flu." The clinic visit was prompted by the onset of diarrhea and lightheadedness. The day before the visit he had stopped at a clinic in Boise, Idaho, where he had been treated for pharyngitis and fever. A *Streptococcus* screen and a Monospot slide test were negative. Treatment consisting of a course of penicillin—250 mg taken orally four times per day—was begun.

(Wood SD, Kristen R, White GL Jr, et al: Maxillary sinusitis—The focus of toxic shock syndrome in a male patient. West J Med 1987 Oct; 147:467-469)

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ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
EBV = Epstein-Barr virus
hpf = high-power field
P_{CO_2} = partial carbon dioxide pressure
PMN = polymorphonuclear neutrophil
P_{O_2} = partial oxygen pressure

Report of a Case

The patient reported having sore throat, nasal congestion, myalgia, arthralgia, fever, fatigue, night sweats and nausea and vomiting for six days and, more recently, diarrhea and light-headedness. He had been working in central Washington reclaiming trout streams until two weeks before the visit. A month before he visited our office he suffered a puncture wound to his right index finger from a blackberry bush; the wound progressed to cellulitis and lymphangitis of his right hand. The wound site was not cultured. The patient was given a ten-day course of cephalexin monohydrate (Keflex)—250 mg four times a day—and there was apparent resolution of the infection. The course of therapy was completed 17 days before the office visit.

He had two syncopal episodes, which were observed, in the office. His blood pressure was 60/0 mm of mercury and his pulse rate was 160 beats per minute. His temperature was 37.8°C (100°F). An intravenous infusion was started and 1 liter of lactated Ringer's solution was infused en route to a local hospital.

His medical history was largely unremarkable, except for the previously noted antibiotic therapy for the finger infection. He said he did not have a history of allergies or sinus problems. He did complain of a headache, however.

On physical examination there were several significant findings. His blood pressure and pulse had risen to 70/40 mm of mercury and 120 per minute, respectively, after the administration of the Ringer's solution, but he was still in a some-

Figure 1.—An anteroposterior view of the patient's sinuses shows a large right maxillary sinus air-fluid level.

what shocky state. He had a notably injected pharynx with a yellow-green nasal drainage and a coated tongue with areas of desquamation. The nares were congested and some exudate was present on the right. There was minimal cervical adenopathy. An examination of the chest and abdomen showed a rapid heart rate and superficial abdominal tenderness in all quadrants. Close examination of the skin showed a healing puncture wound on the right index finger and some erythema on the ventral surface of the right forearm. Transillumination of the sinuses showed no abnormalities.

The admission laboratory studies elicited the following: a leukocyte count of 17,300 per μl with 49 bands, 35 polymorphonuclear neutrophils (PMNs), 5 lymphocytes, 6 monocytes and 5 eosinophils, and toxic granulation; hematocrit 43.2%, and a platelet count of 166,000 per μl. Arterial blood gas determinations with the patient breathing room air showed a partial oxygen pressure (Po_2) of 51 torr, a partial carbon dioxide pressure (Pco_2) of 29 torr and pH of 7.47; these findings improved to a Po_2 of 62 torr, a Pco_2 of 28 torr and a pH of 7.47 with the patient receiving 3 liters per minute of oxygen nasally. The admission serum chemistry values were as follows: sodium 133, potassium 4.7, chloride 96 and bicarbonate 21 mEq per liter; glucose 114, blood urea nitrogen (BUN) 49, creatinine 3.6 and uric acid 6.1 mg per dl; lactic dehydrogenase 159 units per liter; alanine aminotransferase 41 units; albumin 2.7 grams per dl; calcium 7.7 mg per dl, and phosphorus 4 mg per dl. A urinalysis showed a specific gravity of 1.023, pH 5.0, 20+ leukocytes per high-power field (hpf), 5 to 10 erythrocytes per hpf, granular casts and clumps of leukocytes.

The initial chest x-ray film was normal. An electrocardiogram showed sinus tachycardia. Cultures of blood, urine and stool specimens were done, as was a stool assay for *Clostridium difficile* toxin.

The patient was treated with vigorous intravenous fluid replacement, but continued to maintain a pressure of 70/40 mm of mercury. Some 5,170 ml of a 9% normosaline solution was infused into the patient over a 24-hour period. On the second hospital day the patient became tachypneic, with a respiratory rate of 32 per minute; he complained of mild dyspnea. A chest examination showed bibasilar rales, and a repeat chest x-ray film showed infiltrative changes in both lungs. Because of the postnasal drainage and a persistent headache, a complete sinus workup was done, which showed a large right maxillary sinus air-fluid level (Figures 1 and 2).

A repeat complete blood count, meanwhile, showed a leukocyte count of 17,600 per μl, 73 bands, 18 PMNs, 3 lymphocytes, 3 monocytes and 3 eosinophils. The hematocrit was 40.3%. A regimen of nafcillin sodium, 2 grams given intravenously every six hours, gentamicin sulfate, beginning with a 90-mg load and 70 mg given intravenously every eight hours, and erythromycin, 500 mg every six hours, was started.

Swelling and erythema of the patient's hands and feet were noted. A fine petechial rash began to appear on his feet. A tentative diagnosis of the toxic shock syndrome was made, and an infectious disease consultation was sought, as well as an otolaryngology consultation for right maxillary sinus aspiration.

The patient was transferred to the intensive care unit. Several additional tests were done, including a respiratory viral packet,* *Legionella* serology, an Epstein-Barr viral (EBV) titer and a leptospirosis titer.

The otolaryngologist did a needle aspiration of the right maxillary sinus and removed 5 ml of green pus. A Gram's stain showed abundant gram-positive cocci, and the cultures grew pure *Staphylococcus aureus* that produced the toxic shock syndrome toxin and resisted penicillin. Sinus cultures were negative for anaerobes.

Cultures of stool, blood and urine specimens were negative, as were the *C difficile* analysis, the *Legionella* titers, *Leptospira* titers and a skin test for tuberculosis. A stool specimen contained no ova or parasites. The EBV and *Mycoplasma* titers and results of the respiratory viral packet were negative.

On the third day, the gentamicin therapy was discontinued, but administration of nafcillin and erythromycin by mouth was continued. The patient's condition rapidly improved. His BUN level was 29 and creatinine 1.9 mg per dl.

*The packet tests for the following organisms: *Hemophilus influenzae* types a, b and c; *Mycoplasma; Legionella pneumophila; Legionella longbeachae;* atypical *Legionella*-like organisms; respiratory syncytial virus; adenovirus, and *Chlamydia psittaci*.

Figure 2.—A lateral view of the sinus shows an air-fluid level.

Figure 3.—The patient's hands showed desquamation on the eighth day of hospital stay.

The leukocyte count dropped to 11,300 per μl with 49 bands, 35 PMNs, 4 lymphocytes, 2 monocytes and 10 eosinophils. His blood pressure was up to 90/60 mm of mercury, and his urinary output was good. He was transferred back to the general medical floor.

A cough developed, and a repeat chest x-ray film showed moderate bilateral pleural effusions. Sputum cultures were negative. Culture of transudate obtained by a thoracentesis showed no growth. The effusions were believed to be due to the adult respiratory distress syndrome resulting from the toxic shock.

The patient's symptoms continued to resolve, and he was discharged from the hospital on the eighth day. Follow-up sinus and chest x-ray films were clear, and the palms of his hands and soles of his feet were beginning to desquamate at that time (Figure 3). The nafcillin therapy was discontinued, but the patient continued to take erythromycin orally.

Comment

This atypical presentation of the toxic shock syndrome in a man appeared to be due to sinusitis. Although a cutaneous or subcutaneous focus for the syndrome is much more common, given the time frame and apparent resolution of the puncture wound infection after antibiotic therapy, this patient's wound was probably not the origin of his disease. Rather, we are convinced of a sinus origin, and findings of subsequent infectious disease and otolaryngology consultations supported this idea. As a result, we feel it is important for physicians to recognize the possibility of the toxic-shock syndrome in an acutely ill man, even in the absence of cutaneous or subcutaneous infection or of a recent nasal operation with subsequent nasal packing.

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Plasmodium vivax Malaria From Mexico—A Problem in the United States

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THE DIAGNOSIS OF MALARIA is frequently missed in the United States because its symptoms are nonspecific and its onset is uncommon in this country. The disease occurs most commonly in people who have acquired it from an endemic area. Therefore, to diagnose malaria, a travel history must be obtained. In many regions of the country, especially the West, it is common to meet patients whose travel history includes Mexico. Malaria may be overlooked, however, as a cause of febrile illness in this group. The following cases show the need to consider Mexico as a possible source of malaria.

Reports of Cases

Case 1

The patient, a 19-year-old man, came to the emergency department because he had had fever and chills for four days. He was raised in Patizingan, Mexico. He had arrived in the United States three months earlier after traveling by bus from Mexico City to Tijuana and then on to San Diego and East Palo Alto, California. The patient had a transient flulike illness eight months earlier that was treated with penicillin and Contac.* He had been well until four days before presentation, when fevers, chills, a severe headache, myalgias, photophobia, intermittent pleuritic chest pain, pharyngitis, a nonproductive cough, vomiting, abdominal cramping and obstipation developed. He said he did not have dysuria and denied homosexual contacts and cigarette, alcohol or drug use.

On physical examination he appeared acutely ill. His temperature was 40°C (104°F). The blood pressure was 120/70 mm of mercury and the pulse was 130 beats per minute when taken with the patient supine; this changed to a blood pressure of 90/70 mm of mercury and a pulse rate of 160 beats per minute when the patient was sitting. Respirations were 34 per minute and unlabored. The skin, head, ears and eyes were normal. The pharynx was not erythematous. The neck was supple, without lymphadenopathy. The lungs were clear on auscultation. On examination of the heart a 2/6 systolic murmur was heard at the left upper sternal border that did not radiate. The bowel sounds were active, the abdomen was soft and no hepatosplenomegaly was detected. The patient was alert and oriented and showed no focal neurologic signs.

Laboratory studies elicited the following values: a leukocyte count of 3,400 per μl with 24% segmented neutrophils, 65% band forms and 11% neutrophils; the hematocrit was 43.7%. Electrolyte, glucose, blood urea nitrogen and creatinine levels were normal. Results of clotting studies and urinalysis were also normal. On routine examination of the peripheral blood smear, multiple erythrocyte stages of *Plasmodium vivax* were identified.

The patient continued to have orthostatic changes in blood pressure and pulse after receiving four liters of a normal saline

(Brillman J: *Plasmodium vivax* malaria from Mexico—A problem in the United States. West J Med 1987 Oct; 147:469-473)

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*A combination drug, each capsule containing phenylpropanolamine hydrochloride, 75 mg, and chlorpheniramine maleate, 8 mg.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
G6PD = glucose-6-phosphate dehydrogenase
WHO = World Health Organization

solution in the emergency department. He was admitted to hospital and therapy with chloroquine phosphate by mouth was begun. Defervescence occurred within 12 hours of beginning therapy. An assay for glucose-6-phosphate dehydrogenase (G6PD) activity was normal. The patient was discharged on the third hospital day on oral primaquine phosphate therapy.

Case 2

The patient, a 22-year-old woman, presented to the emergency department with vaginal bleeding. She was two months' pregnant and had had vaginal bleeding and abdominal cramping for five days. This was her third pregnancy following one normal vaginal delivery and one spontaneous abortion. High fevers, shaking chills and diaphoresis had begun four days earlier. The patient also had headaches and vomiting, but no arthralgias, myalgias, rashes, cough, diarrhea or dysuria. She had been seen in another emergency department the preceding day, and erythromycin was prescribed, but she did not take it. The patient had moved to the United States from Mexico two years earlier. She had returned from a two-month visit to Mexico nine days before presentation. She had no history of similar symptoms in the past and said she did not use drugs or alcohol or smoke cigarettes.

On physical examination she did not appear to be in acute distress. Her temperature was 39.3°C (102.7°F). With the patient in a supine position, the blood pressure was 100/60 mm of mercury and the pulse rate was 100 beats per minute. With the patient in an upright position, the blood pressure was 90/46 mm of mercury and the pulse rate was 120 beats per minute. Respirations were 20 per minute and unlabored. Skin, head, ears, eyes and throat showed no abnormalities. The neck was supple and the lungs were clear. On cardiac examination a 1/6 nonradiating systolic murmur was heard at the left upper sternal border. There were normal bowel sounds and there was mild tenderness in the left lower quadrant of the abdomen. There was no hepatosplenomegaly. A fetal sac was found in the vaginal vault. There was scant bleeding from the cervical os, but there was no cervical motion tenderness. The uterus was seven to eight weeks' size and was nontender.

Laboratory studies showed a leukocyte count of 5,700 per μl, with 44% segmented neutrophils, 30% band forms, 22% lymphocytes and 4% monocytes; the hematocrit was 28%. A prothrombin time was 14.9 seconds and an activated partial thromboplastin time was 33 seconds. Electrolyte, glucose, blood urea nitrogen and creatinine levels and results of a urinalysis were normal. Because there was a clinical suspicion of malaria, a thin peripheral blood smear was examined and multiple erythrocytic forms of *P vivax* were identified.

The vaginal bleeding subsided, and it was felt that the spontaneous abortion was complete. After receiving five liters of a normal saline solution intravenously, the patient continued to have orthostatic changes in blood pressure and pulse. She was admitted to the hospital, received hydration and oral chloroquine therapy was started. The fever dropped within 12 hours of starting therapy. The G6PD activity was normal, and the patient was discharged the following day on an oral regimen of primaquine. She was seen five days later in gynecology clinic and was noted to be doing well.

Case 3

The patient, a 66-year-old man, went to the emergency department because he had had fever and shaking chills for eight days. He had complained of myalgias, fever and malaise to his physician, who diagnosed influenza. The fevers resolved for two days and the patient went back to work. Four days before presentation, the patient had a temperature of 39°C (102.2°F) and rigors. This resolved for two days and then fever and rigors again occurred. The private physician prescribed cephalexin monohydrate, which the patient took. The symptoms did not abate and the physician asked that the patient be seen in the emergency department. The patient said he did not have symptoms of nausea, vomiting, diarrhea, rashes, cough or dysuria. He had visited Mexico for three weeks and had become ill two weeks after his return. He had traveled in Acapulco and Puerto Escondido, which is 200 miles south of Acapulco. The patient knew that malaria was endemic in that area, but he did not take chemoprophylaxis. He also had served in the South Pacific in 1942, but he did not have medical problems at that time.

On physical examination he appeared mildly ill and had a temperature of 38.5°C (101.3°F). The patient's supine blood pressure was 104/60 mm of mercury and the pulse rate was 140 beats per minute. This changed to a blood pressure of 80/54 mm of mercury and a pulse rate of 160 beats per minute when the patient sat up. Respirations were 24 per minute. The skin and sclerae were icteric. The ears, nose and throat were normal. The neck was supple, without lymphadenopathy. The lungs and heart were normal. The abdomen was soft; the liver edge was felt two fingerbreadths below the right costal margin at the midclavicular line. The patient was alert and without focal neurologic signs.

Laboratory studies showed a leukocyte count of 3,600 per μl, with 16% segmented neutrophils, 70% band forms and 14% lymphocytes. The hematocrit was 39.1%. The electrolyte, glucose, blood urea nitrogen and creatinine levels were normal. The urinalysis was remarkable for the presence of bilirubin. The total bilirubin value was 6.4 mg per dl, an alkaline phosphatase level 194 and aspartate aminotransferase level 12 units per liter. The prothrombin time was 12.3 seconds and the activated partial thromboplastin time was 43.9 seconds. A clinical diagnosis of malaria was made, after which *P vivax* was identified on a blood smear. The patient was admitted to hospital, oral chloroquine therapy was started, and the patient did well in follow-up with his private physician.

Discussion

All the patients presented herein contracted malaria while in Mexico. These are not isolated events, but are part of the steady increase in cases of malaria from Mexico. Over the past five years the number of malaria cases reported to the Centers for Disease Control (CDC) has remained relatively steady,[1] but the percentage of malaria cases from Mexico has more than quadrupled (Table 1).

As Figure 1 illustrates, for 1985, the number of cases of malaria in California is high compared with other states. In 1985, a third of the 1,000 cases of malaria in the United States (367) presented in California.[1] Mexico is becoming an in-

creasingly important source of malaria in California. In 1983 only 20 of 267 (7%) cases of malaria in California were imported from Mexico.[1] In 1985, of the 367 cases of malaria in California, 75, or 20%, derived from Mexico.[1] These 75 cases from California constitute most of the 121 cases of malaria in the United States that were imported from Mexico.[1]

Although malaria was endemic in the United States until the 1940s, its occurrence now in the United States reflects immigration and travel patterns.[2-4] Figure 2 shows cases of malaria reported to the CDC and includes endemic, imported and introduced cases. As the number of endemic cases decreases, three peaks are shown, which reflect malaria imported from Southeast Asia. In the peaks of the early 1950s and late 1960s, malaria was imported by United States military personnel. From 1966 to 1971 the military accounted for 16,872 cases of malaria in the United States.[5] The peak of 1979 to 1981 results from the 1,571 cases of malaria imported by refugees.[5] Malaria is also imported by United States citizens traveling abroad, who were responsible for 9,934 cases of malaria between 1973 and 1984.[1,6] In rare cases, malaria is contracted through a blood transfusion, and 26 of these cases were identified in the United States from 1972 to 1981.[7] Malaria may also be acquired congenitally and through sharing intravenous needles.

Introduced malaria refers to malaria acquired by mosquito transmission in an area where it is not a regular occurrence. This can happen when there are both a high number of mosquito vectors and a population of humans to import malaria. Introduced malaria occurs rarely in the United States and between 1952 and 1981 only 13 cases have been reported.[8-11] Three of these outbreaks were attributed to Mexican agricultural workers.[8] Isolated cases occurring in California in 1980 and 1981 involved exposure to farm workers who had recently arrived from malaria-endemic areas of both India and Mexico.[8,9] No introduced malaria cases were reported from 1981 until 1986, at which time three clusters of introduced *P vivax* malaria were reported in California. The first cluster was two residents of San Diego County who contracted malaria in June and September 1986. Further investigation disclosed 25 Mexican migrant workers with malaria in this area. Also noted were high numbers of *Anopheles freeborni* (an efficient mosquito vector of *P vivax*) to which the affected residents had been exposed. In neither case was there a history of blood transfusion or intravenous drug use. One resident had never traveled to a malaria-endemic region, so local mosquito transmission was confirmed. The place of exposure for the second resident was not certain, as he had traveled to San Blas, Mexico, in September 1985. Malaria is endemic in this region on the Pacific coast.[5,12] A second occurrence of introduced malaria was reported in August in two family members living in Yolo County, California. Neither patient had any risk factors such as a history of travel, blood transfusions or intravenous drug use. There had been a few Mexican agricul-

TABLE 1.—*Total and Mexican-Derived Cases of Malaria in the United States by Year**

Year	Total	Mexico	Percent Mexican
1978	579	15	2.6
1979	825	20	2.4
1980	1,837	20	1.1
1981	1,069	22	2.1
1982	894	55	6.2
1983	803	30	3.7
1984	1,016	62	6.1
1985	1,035	121	11.7

*From the Centers for Disease Control.[1]

TABLE 2.—*Malaria Cases in Mexico by Year**

1981	1982	1983	1984
42,104	49,993	75,029	85,501

*From the Pan American Health Organization.[13]

TABLE 3.—*Malaria Cases in Central America by Year**

Country	Malaria Cases by Year 1981	1984	Net Change
Mexico	42,104	85,501	+43,397
Guatemala	67,994	74,132	+6,138
Belize	2,041	4,117	+2,076
Costa Rica	168	569	+401
Panama	340	125	−215
Nicaragua	17,434	15,702	−1,732
Honduras	49,377	27,332	−22,045
El Salvador	93,187	66,874	−26,313

*From the Pan American Health Organization.[13]

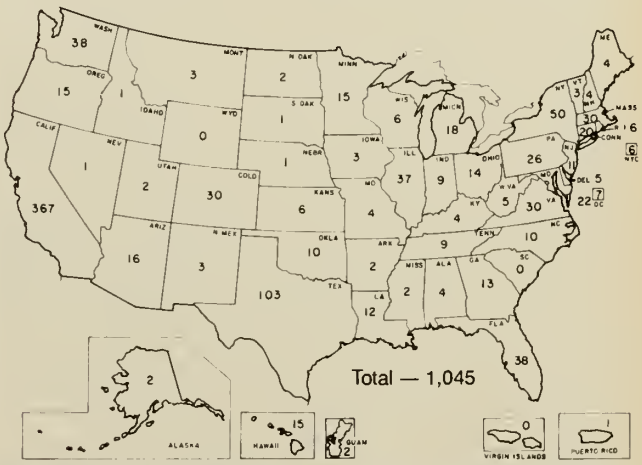

Figure 1.—Geographic distribution of malaria cases with onset in the United States, 1985 (from Centers for Disease Control: Malaria Surveillance Annual Summary 1985[1]).

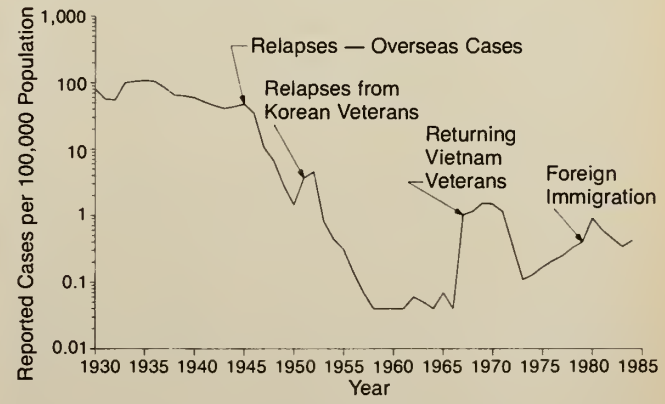

Figure 2.—Malaria—Reported cases per 100,000 population, by year, United States, 1930 to 1984 (from the Centers for Disease Control Annual Summary 1984[4]).

Figure 3.—States in Mexico where malaria prophylaxis is recommended (from the World Health Organization[24]).

tural workers in the area, but these could not be traced. A third episode was reported from Orange County. Again, two family members without any risk factors were identified with malaria. They had traveled to Yolo and San Joaquin counties where high levels of *A freeborni* were measured and cases of malaria had been noted in Mexican agricultural workers (Ronald Roberto, Medical Epidemiologist, Infectious Disease Section, California State Department of Health, oral communication, December 1986).

The increase in both imported and introduced cases of malaria derived from Mexico is most likely related to the documented increase in the incidence of malaria occurring in Mexico. Between 1981 and 1984, the incidence of malaria reported to the World Health Organization (WHO) from Mexico more than doubled (Table 2).[13] This was a greater increase than for any other country in Central America (Table 3).[13]

The number of malaria cases increased in all the Americas by 10% from 1983 to 1984. The difficulties in controlling malaria have been attributed to several factors. One is the increasing physiologic resistance of an important vector, *Anopheles albimanus*, to almost all available insecticides.[13] Mexico is one of a number of countries with serious socioeconomic, political, technical, administrative and financial problems that have hampered adequate malaria control.[13] Malaria risk exists in rural areas of 23 Mexican states. It does not exist in inland states or in Mexico City (Figure 3).[14] Of the 121 cases of malaria imported into the United States, 105 were caused by *P vivax*, 5 cases were caused by *Plasmodium falciparum* and 9 were attributed to *Plasmodium malariae*.[1]

A diagnosis of malaria was initially missed in two of the cases presented above and discovered serendipitously in the other. This is due both to the failure to obtain a complete travel and exposure history and to the nonspecific nature of malaria symptoms.

In case 3, a US resident traveled to an area he knew was malarious. Yet he did not receive malaria prophylaxis, and his physician initially misdiagnosed his illness. This shows the need for greater awareness on the part of travelers and their physicians of the indications for malaria prophylaxis. Furthermore, there have been reports of malaria transmission in nonendemic areas of Mexico, such as Acapulco and Puerto Vallarta.[15] Although the CDC does not recommend chemoprophylaxis for tourists in these areas, it does warn travelers to take measures to reduce their exposure to mosquitos. It also advises physicians to consider malaria as a cause of febrile illness in persons recently returned from resorts on the Pacific coast of Mexico.

Malaria may be difficult to diagnose at first because its symptoms and signs are easily ascribed to other diseases and include high fevers, chills, myalgias, headache, vomiting, hypotension and splenomegaly. Errors in initial diagnosis range from 20% to 83%.[16,17] Fortuitous diagnosis, as in case 1, is common. In one study where 24 patients were initially diagnosed as having a "flulike" syndrome, the diagnosis of malaria was made in 14 patients after laboratory technicians chanced upon malaria parasites in routine blood smears.[16]

The only unique characteristic of malaria is the fever pattern, though it occurs in as few as 30% of cases.[16] The classic pattern involves chills, rigors and a rapidly rising fever that resolves in drenching sweats. These patterns occur every few days and are described as quotidian (every 24 hours), tertian (every 48 hours) and quartan (every 72 hours). The periodicity is related to the synchronous rupture of infected erythrocytes releasing schizonts into the blood. Such periodicity may take days or weeks to develop and may be irregular throughout the course of the disease.[18,19] It may not occur in an initial attack with *P vivax*.

Of the cases reported above, only in case 3 was a periodic fever noted. Case 3 is also notable for jaundice, unusual in *P vivax* malaria, although the patient had no other evident cause of jaundice.

An important complication is shown by case 2, in which the patient underwent a spontaneous abortion. Perinatal wastage in the form of a spontaneous abortion, premature labor, intrauterine growth retardation and neonatal mortality is common in patients with malaria.[17,20] This may be due to sequestration of infected erythrocytes in the placenta.[3,17] Maternal complications such as cerebral malaria and severe anemia are also more likely.[17] Pregnant women, especially when primigravid, may have decreased malarial immunity.[3,20]

Malaria can be effectively prevented and treated. Physicians and other groups dealing with travelers should be familiar with requirements for malaria prophylaxis. The CDC and WHO both publish extensively on this subject.[14,21-24] Current treatment schedules are available in textbooks and in the literature.[18] But because of changing resistance, especially of *P falciparum* to chloroquine, the standard antimalarial regimen, physicians may wish to contact the CDC. The patients whose cases were described earlier did well on what continues to be the current regimen for *P vivax*. All were able to take chloroquine orally, which blocks the erythrocytic stage. Prompt defervescence occurred in all patients within 12 hours of treatment. The G6PD status was determined to prevent potential hemolysis, and patients were discharged on primaquine therapy to prevent relapse from extraerythrocytic parasites. The patients in the cited cases were admitted to hospital. Outpatient treatment, however, may be appropriate for uncomplicated cases of *P vivax*, as is done in endemic areas and in some US medical centers.[18,19]

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Brain Tumors Can Be Subtle

I HAD A PATIENT WHOSE ONLY COMPLAINT was that she used to have beautiful handwriting and now she was writing wee little letters and was forgetting some things. We did a CT scan and she had a frontal lobe brain tumor of a significant size.

—HOLGER RASMUSSEN, MD

Extracted from *Audio-Digest Family Practice*, Vol. 35, No. 17, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206

Correspondence

Pain Control in Cancer Patients

To the Editor: The May 1987 issue included an excellent article on "drug management" of cancer pain by Brigden and Barnett.[1] However, I was misled early in the article to believe all forms of alternative therapies in pain control would be briefly discussed. One alternative that was severely neglected, mentioned once in passing and not even listed under "Other Therapeutic Measures" was palliative radiotherapy (XRT). Nearly half of all radiation oncology patients are being treated palliatively, of whom more than half are being treated for pain palliation.

Let us first turn to their illustrative case regarding a 42-year-old woman with inoperable pancreatic carcinoma. It could have been rewritten just as easily to include palliative XRT, which would have given her the opportunity to become pain-free and drug-free or at least to experience a significant reduction in the severity of her pain requiring less narcotics, as well as the potential for increasing her survival by two to four months.[2]

Early in the article they say "pain due to direct tumor infiltration of bone will often respond well to palliative irradiation, whereas painful breast or prostate metastases may regress dramatically with appropriate hormone therapy." The wording of this sentence implies palliative XRT is not indicated or as effective as hormonal manipulation in breast or prostatic metastases. The major purpose of hormonal therapy is systemic treatment of the cancer in the hope of inducing a remission and prolonging survival with pain palliation as an added benefit. It is true that the use of diethylstilbestrol is noted to provide at least temporary pain relief in 75% of patients with metastatic prostate cancer, which is rarely associated with bone healing on x-ray films,[3] and that luteinizing hormone-releasing hormone-agonist therapy can render rapid short-term relief from painful metastases, but it can cause an initial increase in pain during the first ten days of treatment.[4] Breast cancer patients treated with the use of estrogen, tamoxifen citrate or by surgical ablation experience only a 25% to 50% likelihood of pain relief from symptomatic metastases.[5] In contrast, XRT palliates 73% to 96%, with better relief seen in metastatic breast cancer than prostate or renal carcinoma.[5] Radiographic evidence of bone healing can also be seen several months after completion of a course of XRT, a fact which is the basis for treating all asymptomatic osteolytic bone metastases in weight-bearing bones with radiation.

Reference is also made to narcotic-nonresponsive pain such as degenerative nerve damage and bone destruction. As already discussed, pain due to bone destruction responds very well to XRT, although some may also require a definitive orthopedic surgical procedure. XRT is also used in plexopathies caused by tumor invasion or compression by lymphadenopathy or tumor mass, with good results. Other situations that often develop into narcotic-resistant pain include tumors of and metastases to the adrenals or liver. External beam XRT can attain substantial palliation, although recurrent pain can develop many months later. Stanley Order[6] has been successful in treating hepatic tumors with radioactive yttrium, while other institutions advocate the use of interstitial XRT.

Situations such as compressive or closed-space syndromes in which steroid therapy could be beneficial, I assume in terms of pain control, were mentioned. Although dexamethasone (Decadron) or its equivalent is prescribed routinely in patients with brain tumors, spinal cord compression and superior vena cava syndrome, it is usually given not for its anti-inflammatory effect but to decrease the associated edema by an unknown mechanism. It is important to realize the use of steroids is only a temporizing measure and not a substitute for definitive management. Nevertheless, in these instances a low-dose maintenance regimen of steroids is prescribed throughout a course of XRT to control the already-present edema as well as to prevent XRT-induced edema.

A prophylactic use of XRT in terms of pain control is to deliver one to three XRT treatments to each breast before or at the start of diethylstilbestrol treatment in prostate cancer patients to prevent mastodynia and gynecomastia. Once mastodynia has developed, XRT is less effective.

The moral of the story is that XRT is often the forgotten adjunctive therapy in cancer pain. Remember, not all cancer pain is responsive to analgesia. Although XRT will work best against pain due to direct tumor involvement, it can also be used in many instances when the pain is due to the cancer treatment, such as prophylactic breast irradiation. Although it is not effective against all cancer-related pain, it can palliate metastases in a significant number of patients.

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* * *

Drs Brigden and Barnett Respond

To the Editor: We thank Dr Arlington for her kind comments and certainly agree with her summary of the various uses of radiotherapy as an effective adjunct for controlling cancer pain. Unfortunately, space constraints prohibited us from fully discussing all modalities of cancer pain management. In Canada, radiotherapy tends to be localized in major centres and is not necessarily available to physicians practicing in remote areas. In our article, we concentrated on the proper use of analgesics because, in our experience, this is the major area where many cancer patients continue to receive less than optimal care.

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Tracheostomy Tube Failure

To the Editor: Intermittent or complete tracheostomy tube obstruction secondary to excessive submandibular adipose tissue is not rare in the tracheotomized sleep apnea patient. The article by Rodman and Martin in the July issue[1] described the use of long tracheostomy tubes fashioned from endotracheal tubes to bypass the obstructing tissue. We have used similarly designed tubes but patients often find the long external portion uncomfortable. Additionally, patients with extensive submandibular and neck soft tissue and tracheostomies frequently have difficulties with hygiene, and intertrigo and skin breakdown may develop.

In patients who did not tolerate these special tracheostomy tubes, we have surgically removed the excess, obstructing tissue. A submental lipectomy in a tracheotomized patient with sleep apnea involves making a horizontal apron incision approximately 3 to 4 cm above the stoma. Submental fat and an ellipse of skin are removed. Morbidity is minor and enough soft tissue can be removed to eliminate the obstruction.

Of course, other sources of obstruction should be investigated in a patient with sleep apnea who fails to improve with a tracheostomy. However, submental lipectomy should be considered when the source of obstruction is redundant submandibular tissue.

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REFERENCE

1. Rodman DM, Martin RJ: Tracheostomy tube failure in obstructive sleep apnea. West J Med 1987; 147:41-43

* * *

To the Editor: The article by Rodman and Martin on "Tracheostomy Tube Failure in Obstructive Sleep Apnea" in the July issue[1] is an important contribution to the problem of apnea control. The authors' physiological studies are thorough and their mechanical approach to solve tube failures is novel. However, they leave the sleeping position of their patients—a salient feature of clinical observation—unreported. It is known that people with hypopnea and apnea, like most snorers, change their positions and end up on their backs while asleep. Then they snore. Monitoring of the position is indeed crucial.

This is to call readers' attention to a simple clinical step, originally meant to discourage the snorers—the apnea candidates—from sleeping flat on their backs: Insert half of a soft, spongy rubber ball, which is available in any toy shop, in a little mid-dorsum pocket to be attached to the back of the sleepwear. Some may prefer a 5- by 8-cm firm cushion, 4 cm thick. This serves to forestall snoring and to reduce its long-term risk.

I suggest that Drs Rodman and Miller add the "snore ball" to their clinical sleep testing and to record their patients' recumbencies as part of their sleep patterns.

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Soviet Health Care

To the Editor: In Dr Friedenberg's interesting article, "Soviet Health Care System," in the August issue,[1] he stated that "medical intensive care units, hemodynamic monitoring, vascular and microsurgical techniques and computerized diagnostic modalities—to name a few—have not become a routine part of Soviet medical care."

During my first visit to the Soviet Union in 1969, through the courtesy of A. A. Vishnevski, a vascular surgeon well recognized in the western world, I had the opportunity of observing at least one vascular surgical procedure in Moscow—the replacement of an abdominal aortic aneurysm by a synthetic bifurcation graft. The prosthesis and its use were comparable to the vascular surgery methods in this country.

My second trip to the Soviet Union, with a Harvard alumni group in 1984, included a visit to a cardiovascular surgery institute in Moscow where coronary bypass as well as surgery for congenital heart defects were performed. The monitoring equipment at that institution was advanced and sophisticated, comparable to the best in the United States.

It does not seem likely that the physicians in Leningrad are completely ignorant of what is being achieved in Moscow, less than 400 miles away. More than ten years ago there were, in addition to Dr Vishnevski, two members of the International Cardiovascular Society in Moscow, two in Leningrad, one in Kiev and one in Novosibersk, Siberia.

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Fear of the Unknown

To the Editor: I appreciated the article, "Fear of the Unknown," by E.R.W. Fox, MD, in the June 1987 issue.[1] I was particularly interested in his comments about undue fear of radiation from nuclear power plants. I might point out that there was an excellent article in the March 1983 issue by William R. Hendee, PhD, entitled "Real and Perceived Risks of Medical Radiation Exposure."[2] It includes a graph that shows the real and perceived risks of smoking, motor vehicles, electric power, swimming and x-rays, as compared to nuclear power, by several different groups. It was interesting to note that the fear of nuclear power far outstripped any risks as yet demonstrated, even with the Chernobyl disaster. Perceived risks for all the other factors were greatly underestimated by nearly all groups.

An article in the March 1986 *Reader's Digest* points out the high level of radioactivity associated with smoking tobacco. Tobacco smoke contains both lead 210, which has a weak β-radiation and a long half-life of more than 20 years, and, more important, polonium 210, which emits ionizing α-radiation. In the April 24, 1987, issue of the *Journal of the American Medical Association,* there is an interesting letter from Hebrew University in Jerusalem, pointing out that a smoker may be exposed to as much as 7 mrem of radiation per cigarette.[3] They predicted four extra cancer deaths in the

Israeli population over 50 years from the Chernobyl fallout and more than 80,000 excess cancer deaths due to smoking, the majority of which may possibly be due to tobacco-related radiation. They also pointed out that about 75% of the radioactivity in cigarettes has been found in sidestream smoke.

Dr Fox again points to an interesting paradox in human thinking. This is well illustrated by the current fear of AIDS (acquired immunodeficiency syndrome), which is indeed a terrible problem. It is estimated that the death toll may be as high as 50,000 per year by 1990. We are greatly concerned about this, and yet we show little concern over the fact that we have 1,000 premature deaths per day in this country from smoking cigarettes, due to their association with many types of cancer, atherosclerosis with its attendant heart attack and stroke and chronic pulmonary disease. Surely we need a massive educational campaign to educate humanoids about the hazards of using recreational drugs, tobacco, alcohol, marijuana and other inappropriate life-style and dietary practices that adversely affect our good health.

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Signs of Physician Impairment

MANY NEGATIVE views of the world may come out in the medical office. Certain physicians may leave the office, only to end up taking an extended lunch hour or lunch break because they have had one or two drinks. They may then call in and ask "Hey, any emergencies? Well look, could you have Doctor so-and-so cover for me?" Many times, their appointment schedules also become bizarre and colleagues start making excuses for them because these physicians try to enlist their sympathy by confiding all their problems to them. And if colleagues become sympathetic, they are encouraging that "poor me" syndrome, which goes something like this: "poor me, poor me, pour me another drink," and the next thing colleagues know, they are part of the conspiracy.

It is really a tendency on our part, sometimes, to wait this guy out and accept the excuses. "I know it's going to get better" and he divorces his wife and you just know it is going to get better now. But it doesn't, and it doesn't get better with his girlfriend or girlfriends. You may also start to see some complaints and some rumors with the office staff: "I'm worried about Doctor Jones." They don't come out and say "I think he's an alcoholic or an addict," but they may give you some connotations. He may be down on the office staff a lot. They may be resigning, there may be some office discord, and all this may tend to lead back to him. And some of these physicians get into creative record keeping in the office, especially concerning some of the controlled substances.

Physicians who become impaired tend to take geographical cures. "Things are really bad here—it's the town, it's the staff, it's the hospital. I think I'll move to another location." They do and they look real good, and then things get crummy again and they move to another location. So they may hop around a lot. There may be some difficulty verifying references. These physicians also may be reluctant to have lab tests done—especially urinalysis; they may fear they will be given a drug screen. The job they are seeking also may be incompatible with their training. A board-certified cardiologist who comes in with an application for a $30,000-a-year job at a medical clinic or a neurosurgeon who shows up wanting to work the emergency room may have problems. There may be a need to look at some of the backgrounds. If it seems too good to be true, it probably is too good to be true.

There may or may not be malpractice issues, but the impaired physician is certainly an increased risk for a malpractice situation.

—LOUIS CATALDIE, MD

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Topics in Primary Care Medicine

Exercise in the Elderly

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

Fewer than a third of the 25 million Americans older than 65 years exercises regularly. Scientific evidence, however, increasingly suggests a health benefit of physical activity for all ages. Policy groups such as the American Medical Association and the Public Health Service now explicitly recommend regular exercise for seniors.

The goals of exercise in the elderly differ from those in younger groups. In the "old-old"—those older than 75—the emphasis is on maintaining flexibility, strength, coordination and balance, not on aerobic training. Walking and range-of-motion exercises are examples of appropriate activities for previously sedentary members of this group. In the "young-old"—those aged 65 to 75 years—exercise may also include moderate aerobic conditioning. Primary care physicians should individually tailor activity prescriptions based on a patient's previous exercise experience, current activity, general physical condition and medical history.

Exercise and Health Benefits

About 35% of noninstitutionalized elderly between the ages of 65 and 74 describe themselves as limited in some activity. While some of this limitation results from chronic conditions or the aging process itself, a substantial portion is due to disuse. In sedentary elderly, their aerobic capacity is so low that simple activities such as making beds or dressing and undressing may represent 50% of their maximal capacity. Because working at this intensity for longer than an hour causes significant fatigue, even a small—10% to 15%—improvement in the work capacity of unfit seniors could improve functional ability, quality of life and continued independence. Longitudinal studies show that habitually active seniors slow their age-related aerobic decline and that exercise training in the elderly produces a significant increase in work capacity. In very sedentary persons—those who seldom ambulate outside the home—a small increment in physical activity produces a relatively greater benefit than in the more fit.

Some medical conditions may resolve with exercise. Obesity is diminished through increased caloric expenditure, appetite suppression and an increased metabolic rate. The blood pressure declines independent of changes in body weight, and cardiac efficiency increases. Diabetic persons may benefit through weight reduction and improved glucose use by exercising muscles. Physical activity retards the progression of osteoporosis. Muscle flexibility, coordination, mechanical efficiency and strength increase. Improved muscle function in turn protects vulnerable joints, thus enhancing overall physical ability.

A sense of well-being and self-image are enhanced with regular exercise, resulting both from social interaction and physical training. Some researchers show enhanced mood and aspects of cognitive function. Finally, sleep patterns and bowel function are improved and anxiety lessened, particularly somatic manifestations such as muscle tension.

Exercise-Associated Risks

The most serious risks of exercise are cardiovascular, including sudden death. Such rare events are most likely to occur in those with decreased left ventricular function and active ischemia. A survey of cardiac rehabilitation centers showed a rate of nonfatal cardiac arrest of 1 per 34,673 patient exercise hours, with fatal arrests occurring 1 per 116,402 patient exercise hours. No comparable data exist for community-dwelling elderly. Although the risk of sudden death rises with exercise intensity, habitually active persons are at a lower risk than those who are sedentary when exertion is comparable. Because inactivity produces its own medical complications, risk versus benefits must be assessed individually.

The danger of falls and other musculoskeletal complications must also be evaluated. Limitations identified by medical examination, such as poor vision, must modify the exercise prescription. Shock-absorbing shoes with traction soles (such as running shoes) are indicated for all active elderly. Exercycles or chair exercises are indicated for persons with an unsteady gait; pool exercises are appropriate for those with significant arthritis. Proper warm-up, gentle stretching and a gradual onset of low-impact activity reduce adverse

(Wheat ME: Exercise in the elderly. West J Med 1987 Oct; 147:477-480)

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ABBREVIATIONS USED IN TEXT

HRR = heart rate reserve
MHR = maximum heart rate
RHR = resting heart rate

musculoskeletal effects. Most community-dwelling elderly are able to walk. This, with flexibility exercises, is an excellent way to maintain the ability to perform daily activities.

Evaluating an Exercise Candidate

Preexercise screening assures that an elderly person is given an appropriate activity regimen. Cardiovascular training should not be an automatic goal of exercise for all elderly, but is appropriate for many "young-old" and for seniors older than 75 who have continued to be physically active. Critical aspects of assessment include previous and current levels of activity, cardiovascular and mental status, balance and gait stability. Practitioners must be aware of subtle cognitive declines that might limit someone's ability to follow an exercise prescription, as well as sensory impairment or balance problems that could predispose to falls. The history includes the above areas and respiratory symptoms, musculoskeletal complaints and drug history (all medications plus alcohol, tobacco and caffeine use). Nutritional status and weight are also evaluated. The physical examination focuses on the cardiovascular and pulmonary systems; vision and mental state; the musculoskeletal system, including range of motion, and gait stability. The physician must observe a patient walking and know his or her current capacity, either from a reliable history or direct observation. Laboratory tests include a resting electrocardiogram, hematocrit, glucose level and urinalysis for new patients, as well as any tests indicated by the history and physical examination. Those taking diuretics should have a potassium level checked. Diabetic persons need their risk of hypoglycemia assessed.

Patients without evidence of coronary artery or other cardiovascular disease do not require exercise stress testing if the only proposed exercise is walking. If more intense training is planned, then stress testing is recommended. Of community volunteers for unsupervised aerobic exercise programs of moderate intensity (70% to 85% of maximal heart rate), 10% to 43% are excluded by a combination of a history and findings of a physical examination, laboratory tests, resting electrocardiogram and stress testing, and 70% to 80% of these are excluded before the stress test.

Exercise Stress Testing

Preexercise stress testing provides a known, graded stress under continuous electrocardiographic monitoring to identify a safe heart rate range during exercise regardless of the presence of coronary artery disease. Maximal stress testing is not necessary, although protocols should reach at least 85% of the age-predicted maximal heart rate. Indications for terminating a test before achieving 85% of the maximal heart rate are listed in Table 1.

Treadmills or bicycle ergometers may be used, although walking on a treadmill may be difficult for those with balance problems. The Naughton or Balke protocols are better tolerated than the Bruce protocol. Bicycle ergometers are an appropriate alternative for patients with gait or visual disorders, but because cycling is a less familiar exercise than walking, local muscle fatigue may limit endurance before an adequate heart rate is reached.

ST-segment changes are most indicative of coronary disease if they occur with angina, arrhythmias, abnormal blood pressure response or at low exertion levels. Patients in whom significant ST-segment depression or hypotension develops in the first three minutes of exercise have a substantial risk of high-level coronary artery disease (triple-vessel or left main) and require a prompt diagnostic follow-up.

Symptoms and electrocardiographic changes occurring near maximal exertion are relative contraindications to exercise. One may prescribe activity at a lower heart rate, generally 75% of that at which abnormalities occur. Such persons should participate initially in a medically supervised program.

Seniors in whom significant ST-segment depression develops without chest pain, particularly at higher levels of exertion, comprise the most difficult diagnostic category. A substantial number of positive exercise stress tests—25% to 50%—have been recorded in asymptomatic elderly, particularly women. Of these positive tests, 25% to 45% are negative on repeat testing or the ST-segment depression resolves with conditioning. Table 2 lists causes of false-positive stress tests.

TABLE 1.—*Criteria for Stress Test Termination**

- Premature ventricular contractions
  - Multifocal
  - In pairs, with increasing frequency
  - Ventricular tachycardia—3 or more in a row
- Blood pressure
  - Fall in systolic pressure 10 mm of mercury or more
  - Systolic pressure >250 mm of mercury
  - Diastolic pressure >115 mm of mercury
- New-onset atrial tachycardia, fibrillation or flutter
- Second- or third-degree heart block
- Angina, faintness, pronounced fatigue, dyspnea, nausea, pallor, confusion
- Claudication or significant musculoskeletal pain
- Significant ST-segment depression—greater than 1 mm of horizontal or downsloping ST-segment depression at 80 ms from J point, or greater than 2 mm of upsloping ST-segment depression at 80 ms from J point
- ST-segment elevation
- Achievement of 85% or more of age-predicted maximal heart rate

*Adapted from Posner et al (*Am J Cardiol* 1986; 57:56C).

TABLE 2.—*Causes of "False-Positive" ST-Segment Changes During Exercise Stress Testing**

- Hyperventilation
- Abnormal ventricular depolarization-repolarization
  - Left ventricular hypertrophy
  - Left-sided intraventricular conduction delays
  - Wolff-Parkinson-White syndrome
- Other cardiac abnormalities—valvular disease, asymmetric septal hypertrophy
  - Vasoregulatory abnormalities
  - Digitalis toxicity
  - Hypokalemia
  - ST-segment depression at rest

*Adapted from Shepard ("Prognostic Value of Exercise Testing for Ischaemic Heart Disease," *Br J Sports Med* 1982; 16:220-229).

Unless the medical and family histories strongly indicate coronary artery disease, it is appropriate to prescribe exercise at a heart rate not to exceed 75% of that at which asymptomatic abnormalities occurred. Men and high-risk women should begin in a supervised setting; low- or average-risk women may not require supervision. All should be instructed in the danger signs of ischemia (to be described) and told to stop exercising and to return for further evaluation if such signs occur. If the history suggests a high-risk patient, or abnormalities occur with moderate exertion, noninvasive tests such as exercise thallium scintigraphy may clarify the diagnosis.

Table 3 lists common drugs that may affect an exercise program. Medication requirements in patients with diabetes mellitus may decrease. Persons with insulin-requiring diabetes should not inject insulin directly into muscle groups used in exercise. The increased blood flow may enhance uptake and precipitate hypoglycemia. Excessive caffeine use may predispose to arrhythmias. Patients taking drugs that can cause orthostasis should have lying and standing blood pressures checked.

Exercise Prescription

Exercise programs should be individually tailored. When aerobic conditioning is desired, one program that improves cardiovascular capacity in inactive elderly aged 65 to 75 years is based on the heart rate reserve, calculated by subtracting the maximum heart rate (MHR) from the resting heart rate (RHR). A training response occurs when 30% to 45% of the heart rate reserve is added to the resting heart rate. This is the target heart rate range, about 65% to 80% of the predicted maximum heart rate, somewhat lower than the 70% to 85% of the MHR recommended by the American Heart Association for aerobic conditioning. One calculates the training heart rate range for a 70-year-old person with a resting heart rate of 84 beats per minute as follows:

1. Maximal heart rate = 220 minus age (years):
   $220 - 70 = 150$
2. MHR − RHR = heart rate reserve (HRR):
   $150 - 84 = 66$
3. Determine 30% and 45% of the HRR and add to resting heart rate:
   $30\% \times 66 = 20; 45\% \times 66 = 30.$
   $84 + (20 \text{ to } 30) = 104 \text{ to } 114$
4. Training heart rate range = 104 to 114 beats per minute.

Unfit persons with a higher resting heart rate and a lower heart rate reserve require a smaller increment to reach the training range.

Exercisers should take their pulse the first ten seconds immediately after ceasing activity (exercise heart rates fall off rapidly) and be taught to adjust the intensity of exercise. If palpation shows a heart rate below the training level, the intensity is increased. For example, if the exercise is walking, a brisker pace is adopted. Conversely, if the heart rate is above the target range, the intensity is reduced. Participants' calculations of actual heart rate should be checked initially by a monitor or a trained person.

All sessions begin with five to ten minutes of gentle stretching and flexibility exercises of the neck, trunk and limbs. Sitting stretches to reach the toes, neck rotation, hamstring, quadriceps and sideways trunk stretches are all appropriate. The exerciser should hold the stretch (just beyond what is comfortable) for ten seconds and *should not bounce.* Bouncing increases muscle tension by stimulating antagonist muscles. Light limb exercises follow. Such warm-up periods decrease the risk of musculoskeletal complications and reduce the incidence of myocardial ischemia during exercise. Cool-down and flexibility exercises are repeated after the exercise program. Muscles tend to shorten during vigorous exertion; a post-workout stretch decreases the incidence of muscle cramps. When aerobic conditioning is contraindicated, stretching and range-of-motion activities can be prescribed alone or before and after a period of walking.

Most studies show an optimal effect of training with a 30-minute period of increased heart rate three times per week. Lower intensity exercise—50% to 60% MHR—may produce a training effect if the duration is extended. Less frequent exercise is unlikely to improve fitness. Exercising more than five times per week increases the likelihood of musculoskeletal injury; high-intensity exercise increases both musculoskeletal and cardiovascular risks. Initially most sedentary elderly will be unable to sustain a training heart rate for 30 minutes. One begins gradually, for example, alternating 2 to 3 minutes of increased activity with a 2- to 3-minute recovery period over 15 minutes. Increase the total exercise period by 5 to 10 minutes per week until the 30-minute goal is reached. The activity periods can then be increased by 1 to 2 minutes each week until the target heart rate can be sustained for 30 minutes.

TABLE 3.—*Common Drugs That May Affect an Exercise Program*

Drug	*Effects*
Hypnotics	Orthostasis and falls
Tranquilizers	
Antihypertensives	
Diuretics	Hypokalemia→arrhythmias
	Dehydration→orthostasis and falls, thermoregulatory disturbance
Antidepressants	Orthostasis and falls, arrhythmias
Insulin, oral hypoglycemics	Hypoglycemia
β-Blockers	Decreased heart rate, fatigue

TABLE 4.—*Energy Requirement for Common Activities**

Activity	*Mets*	*Kcal/hr*
Walking at 2 to 3 miles per hour (mph)	2 to 4	180 to 300
Cycling (level) at 6 mph		
Light stretching exercises		
Swimming (with float board)		
Light to moderate housework		
Walking at 4 mph	5 to 6	300 to 360
Cycling at 8 mph		
Golf (walking, pulling cart)		
Light calisthenics		
Swimming (treading water)		
Heavy housework or yard work		
Walk-jog at 5 mph	7 to 8	420 to 480
Swimming (½ mile in 30 minutes)		
Cycling at 11 to 12 mph		
Recreational tennis		
Hiking		

*Adapted from Hanson PG, Giese MD, Corliss RJ ("Clinical Guidelines for Exercise Training," *Postgrad Med* 1980 Jan; 67:120-138).

In a previously inactive "old-old" person, a lower intensity and more frequent but shorter periods of activity are advised—such as a goal of 15 to 20 minutes of walking six times a week. Use shorter intervals to build endurance; for example, alternate 30 seconds of activity with 30 seconds of rest. Increase the activity intervals by 30 to 60 seconds per week as endurance improves. In a very unfit person, the work capacity may be so low that conditioning occurs as a by-product of programs that would produce no training benefit in a more active person. Clinical signs of improved aerobic capacity include a lower resting heart rate and decreased perceived exertion. The distance walked in six minutes can also be used to assess fitness. Activity intensity is often expressed in mets (one met is the oxygen uptake at rest, about 3.5 ml per kg per minute). Maximal oxygen uptake (met capacity) can be derived from stress test data. When the heart rate response is normal, an 80% MHR corresponds to 70% of met capacity. Table 4 shows the met level of some common activities.

A *written* prescription should detail the activity(s) recommended for each patient, including the initial intensity, duration and frequency and how to increase the activity as fitness improves. Include instructions to stop exercising promptly and see a physician should effort-related symptoms of chest pain, pronounced dyspnea, dizziness, claudication or extreme fatigue develop. Exercisers are also told to drink ample fluids and to refrain from exercise in extreme heat and cold.

Jogging may be inappropriate for elderly persons not already accustomed to this activity. Walking, cycling, dancing and swimming all provide excellent conditioning (aerobic or otherwise) with less stress on the low back and lower extremity joints. Physical activity should also be included in a person's daily pattern. For example, a shopping cart may enable someone to shop on foot instead of in a car, or one can walk up a flight of stairs instead of taking the elevator. James Mason, Director of the Centers for Disease Control, has said, "Marathons are not for everybody, but walking around the block probably is."

Medically supervised exercise programs can be located through hospital or cardiac rehabilitation programs, the American Heart Association or senior groups such as college extended-learning programs. Persons with a history of cardiac disease and those with a positive stress test that still permits exercise should begin an exercise more vigorous than walking in a supervised setting. If no adverse effects occur, they may continue independently at the same exercise intensity after three to six months of conditioning. Very frail elderly, those who cannot walk several blocks without difficulty and persons with cognitive impairment precluding reliable self-monitoring, should also begin any significant increase in activity under supervision. If musculoskeletal (overuse) symptoms occur, the activity is stopped or changed—such as swimming instead of jogging—until the person is pain-free. If injury or illness causes a cessation of exercise for more than a week, the activity is resumed at a lower intensity.

One may prescribe exercise individually or in a group setting. Except for persons requiring supervision, both are appropriate. The social interaction of a group setting may enhance psychological gains and adherence to the exercise program. Adherence is also fostered by picking an activity the patient likes, setting attainable goals and providing encouragement and reinforcement during training and at follow-up visits.

With appropriate screening and individualized exercise prescription, regular physical activity can and should be incorporated into the life-style of senior citizens. Increases in activity among sedentary persons have the potential to bring major benefits in functional capacity, a sense of well-being and other health outcomes.

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Medical Schools of the West

Oregon Health Sciences University School of Medicine Celebrates Centennial

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One of a continuing series of reports from the medical schools of the West

Just 100 years ago this fall, the inaugural class of the University of Oregon Medical School gathered for the first time in the school's lone building—a two-room converted grocery store in northwest Portland. Eight practicing physicians lectured part-time for little or no money. In all, 18 men attended classes in its one lecture room; cadavers were hauled through a trapdoor to the dissecting room above with a block and tackle.

Today that school's direct descendant, the Oregon Health Sciences University (OHSU) School of Medicine, is an integral part of a $200 million, 26-building academic health complex that includes schools of Dentistry and Nursing, University Hospital, Doernbecher Children's Hospital, University Clinics (medical and dental), a Crippled Children's Division and a new research unit—the Vollum Institute for Advanced Biomedical Research.

Now located on a hilltop site, the campus overlooks the city of Portland. The school's student body has grown to 500—with this year's entering class nearly 50% female. Faculty members now number 500, with more than 1,000 practicing clinicians who serve as volunteer faculty members.

In 1887 admission to the school required knowledge of the "common English branches, including reading, writing, spelling, grammar, geography, arithmetic and so forth." Today it involves at least three years of premedical study, entrance examinations, proof of character and personal interviews.

Training in 1887 lasted two years and had to include "two full courses of lectures and at least one course of practical anatomy and clinical instruction." Today the curriculum includes subjects such as medical genetics, immunology, microbiology and radiographic diagnosis. Under consideration are core courses that reflect societal concerns such as occupational diseases, medical ethics and a growing geriatric population.

In 1887 medical research in Oregon did not exist in the modern sense. Bacteriology was just emerging as a field of medical instruction when the school was founded, and, until 1892, microscopes in the medical school lacked an oil immersion lens.

The OHSU School of Medicine today boasts spacious laboratories, the most advanced equipment and a vital research program. Here, too, tomorrow's biomedical researchers can pursue master of sciences and doctoral degrees in anatomy, biochemistry, medical genetics, medical psychology, microbiology, pathology, pharmacology and physiology. Also available are baccalaureate and master's degree programs in medical technology and allied health programs in advanced paramedics, dietetics, nuclear medicine, radiation therapy, x-ray and ultrasound technology and alcohol counseling.

In education, patient care, public service and research, the OHSU School of Medicine has made enormous strides in 100 years. The story behind its evolution is one of men and women dedicated to improving the quality of medical education and health care in Oregon.

Willamette Medical Department

The mid-19th century found Oregon without enough well-trained physicians to meet the needs of a rapidly growing population. So members of the medical department at Willamette University in Salem, a private institution, began the state's first formal medical education program in 1867. The department relocated to Portland in 1878, where classes were held in a few rented rooms above a livery stable. Admission requirements consisted of little more than possession of a "good English education."

Eight years later the department expanded, moving to an elaborate Victorian building that contained a 150-seat auditorium, a dissecting room with 20 tables and a refrigerator large enough to store 30 cadavers (Figure 1). But classes no sooner began when four physicians resigned to protest a faculty reorganization and the appointment of a new chair of obstetrics. The four dissenters and four other local physicians were granted a charter in June 1887 by the Board of Regents of the University of Oregon to open a state medical school in Portland, the forerunner of OHSU's School of Medicine.

The First Quarter Century

Simeon E. Josephi, MD, one of the four dissenters, was elected first dean of the new medical school. A graduate of Toland Medical School in San Francisco, Dr Josephi specialized in obstetrics and diseases of the mind and nervous system. He was described by a contemporary as a "good

(Leonhardt FW, Ward DE: Oregon Health Sciences University School of Medicine celebrates centennial. West J Med 1987 Oct; 147:481-485)

From the Office of University Communications, Oregon Health Sciences University, Portland.
Reprints not available.

looking man of about ordinary height, of graceful form and figure, jet black hair and whiskers, with mild brown eyes, a pleasant voice and suave manner, a good talker, intelligent, with quick perceptive faculties, always faultlessly dressed"—invaluable attributes for the man who would guide the fledgling school through its first critical quarter century.

Classes began in the fall of 1887 in a former grocery store on the Good Samaritan Hospital grounds in northwest Portland. Coursework included lessons in microscopy, histology and physiology, but the first actual laboratory class in bacteriology was not held until 1892, when Dr A. E. Mackay displayed the first tuberculosis bacillus seen under a microscope in the Pacific Northwest.

By 1898, when the school adopted the requirements of the Association of American Medical Colleges, the course of study had been lengthened to four years and studies were being graded. A knowledge of physics and elementary Latin was required for admission. Laboratory work was required but, except for some microscopes, equipment was lacking (Figure 2). Lectures were sporadic as many instructors understandably tended first to their private practices. Aside from a small amount from the state, school revenues were derived almost exclusively from student fees, which were insufficient to pay staff and acquire books and laboratory equipment. At the close of 1900, the school had a surplus of $4,154.36 from receipts of $7,171. The surplus was distributed among 25 lecturers who had given 932 lectures, so they received less than $5 per lecture.

In 1905 the American Medical Association raised its teaching and equipment standards for medical schools, but inadequate funding prevented the dean from meeting these demands and the school's closure seemed imminent. A desperate faculty appealed to the University of Oregon's Board of Regents. It paid off. The board increased the school's annual appropriation from $1,000 to $2,500.

Bolstered by increased financial support, the school appointed its first full-time instructor. At a conference in Chicago on medical education in 1910, it was included in the list of class A institutions. By 1912, the medical school had a full-time laboratory staff and a dispensary organized for the instruction of students (Figures 3 and 4).

Figure 1.—Although admission requirements and curriculum have changed dramatically, education has been the Oregon Health Sciences University School of Medicine's primary mission since the school began in 1887. Medical students in the late 1800s were required to attend two courses of lectures and at least one course of practical anatomy (shown above in a circa 1920 photo) and clinical instruction. Above is the anatomy laboratory of the medical school when it was located at 23rd and Lovejoy Streets of Portland in the late 1800s.

'Mackenzie's Folly'

Dean Josephi was succeeded in 1912 by another of the school's founders, Kenneth J. Mackenzie, MD. The new dean was vigorous, forceful, one of the best known physicians in the region and chief surgeon of the Oregon Railway and Navigation Company. He realized that the school needed larger quarters and better equipped laboratories. Dean Mackenzie envisioned a thriving medical center away from the city's noise and grime, and he found a way to do it—he persuaded the Oregon Railway and Navigation Company to donate to the school 20 acres of land on Marquam Hill, the site of the present-day campus (Figure 5).

Building a medical school accessible only by a winding wagon road and situated a mile and a half from the center of the city was daring, and the school was often referred to as "Mackenzie's Folly." But the dean worked unceasingly to develop his folly into a first-rate medical education center.

The railroad's donation of land in 1914 was followed by

Figure 2.—In 1887 physicians in Oregon were largely borrowers of medical knowledge. Laboratories existed in the crude sense, as seen above, but with the development of laboratory science in the late 1800s, research mushroomed and the School of Medicine has been at the forefront of many medical advances.

Figure 3.—Pictured in the photo is the physiology laboratory of the Oregon Health Sciences University School of Medicine in the north attic on Lovejoy Street as it appeared in 1912. The beginnings of the library can be seen in the background.

a legislative appropriation of $50,000 for construction of a three-story Medical Science Building, now called Mackenzie Hall, that was completed in 1919. The first class on the hill included 50 students, mostly ex-servicemen, and 10 full-time faculty members.

At the same time, a new county hospital was urgently needed to replace the one located in Portland. Knowing that clinical facilities adjacent to the school would benefit the students, Dean Mackenzie offered nine acres on campus for a general charity county hospital and nurses' dormitory. The Multnomah County commissioners accepted the offer and agreed to an affiliation between the hospital and the medical school for clinical teaching. Construction of the new Multnomah County Hospital on Marquam Hill was well under way when the dean died suddenly in 1920.

Entering the Modern Age

The new dean, Richard B. Dillehunt, MD, shared Mackenzie's vision of a modern medical education center. Affectionately known as "Dilly," the dean was chief surgeon of the Shriners' Hospital for Crippled Children for 19 years. A contemporary said of Dean Dillehunt, "Children are not abashed by the great height and quite noble girth that encase his voice. He may not utterly hate being complimented, but his remark on these occasions is, 'Oh yes, isn't it nice to be nice?'"

Figure 4.—Caring for patients has been a critical aspect of educating tomorrow's physicians. Higher standards for patient care led to improved patient care facilities for students. In 1909 arrangements were made to use the Multnomah County Hospital for teaching purposes, and in 1910 the school became affiliated with its first outpatient facility, the People's Institute and Free Dispensary in downtown Portland.

Figure 5.—A parcel of 20 acres of land was donated in 1914 on Marquam Hill, the site of the present-day Oregon Health Sciences University campus. Construction of the three-story Medical Science Building in the photograph was completed in 1919. There were 50 students, mostly ex-servicemen, in that first class on the hill, and 10 full-time faculty members.

In 1924, an additional 88 acres of adjoining land was donated to the campus by a Portland family, 25 acres of it being deeded to the United States government as a site for a veterans' hospital. In 1926 the original 70-bed Doernbecher Children's Hospital, now part of the Outpatient Clinic, was completed. A gift of $400,000 from the General Education Board of New York in 1931 made possible a modern outpatient clinic on campus that improved both patient care and the quality of education. The following year, the University of Oregon's nursing program was transferred to the medical school as the Department of Nursing Education (Figure 6).

Research took on added significance during Dean Dillehunt's tenure. A faculty member wrote in 1924 that "our medical school is known and will be known by the research that comes from it." Medical school researchers studied the nervous system, intestinal obstruction, heart disease, the relation between infection of the gallbladder and pernicious anemia and the "increasing predominance of goiter among the people of the Pacific Northwest." One physician noted in 1925 that autopsy studies showed "a much greater frequency of coronary obstruction than has hitherto been imagined" (Figure 7).

But library facilities were "fast falling short of the research pace," according to one faculty member. "As our library is limited, so will research be handicapped."

As late as 1918 books were stored in a locked room the size of a closet, to which only the janitor had the key. Larger quarters became available in 1922 with completion of the main unit of the medical school building. The state legislature in 1929 required that a portion of physicians' annual registration fees be provided to the library, supplementing its regular budget. In 1939 the medical school library and auditorium were completed.

Ill health forced Dean Dillehunt into semiretirement in 1943, and David W. E. Baird, MD, was appointed to take his place.

Figure 6.—Physicians in 1920 used the x-ray viewer (far left corner) when diagnosing patients' disorders.

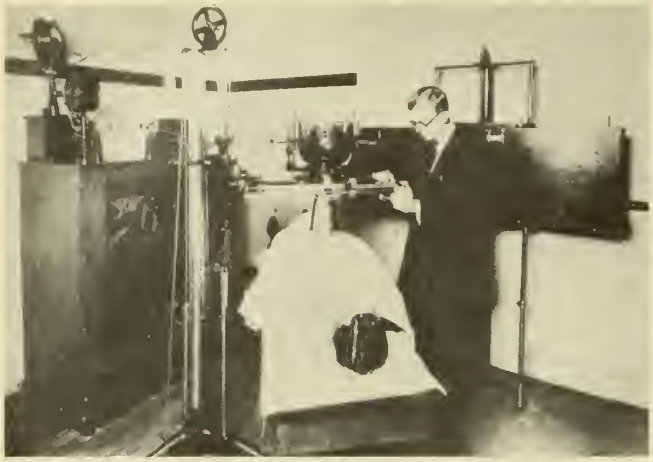

Figure 7.—Physicians in the early 1900s did not have the benefit of today's computed tomographic scanner and ultrasound for diagnostic purposes.

Figure 8.—Today the School of Medicine is part of the $200 million, 26-building Oregon Health Sciences University. Now located on a 116-acre hilltop, the campus overlooks the city of Portland, with Mount Hood in the background.

Continued Growth

Dean Baird, a graduate of the University of Oregon Medical School, had been an internist in private practice with years of experience as a hospital administrator, teacher and researcher. Again, updating and expansion of the school was necessary. The availability of state funds after World War II helped to replace worn-out research and clinical equipment with new and modern equipment. During this time, the number of faculty increased from 10 in the 1920s to 125 in the 1950s.

In 1949, Baird Hall was built to house basic science departments and administrative offices. The Crippled Children's Division, which today provides diagnosis, treatment and rehabilitation for handicapped people throughout the state, was built in 1954.

A top priority was the medical school's need for its own teaching hospital where educational and research activities could be integrated with patient care. This need was met in 1955 when a 14-story Medical School Teaching Hospital was built into a ravine on the south side of the hill. It quickly became the school's main clinical teaching facility. In 1956, Doernbecher Memorial Hospital for Children moved into its current location on the top two floors of the medical school hospital. Today Doernbecher contains both a neonatal intensive care center and a newly remodeled pediatric intensive care center.

The University of Oregon School of Dentistry joined the burgeoning campus when the building to house it was completed in 1956; in 1960 the Department of Nursing Education became the University of Oregon School of Nursing. The nursing school, administered by its own dean, remained a part of the School of Medicine until 1974 when it was established as a separate school.

The 1960s brought continued growth. The Medical Research Building was built, the emergency department renovated and the library expanded. A six-story addition that included a 20-bed psychiatric crisis unit and seven state-of-the-art operating rooms was added to the county hospital.

Dean Baird was succeeded in 1968 by Dr Charles N. Holman, who served as dean for seven years. As medical student, resident in internal medicine, teacher and hospital administrator, Dr Holman's association with the medical school spanned 36 years. Holman took over the helm at a time when many were asking, "What ails medical schools?"

The new dean recognized that the medical school needed to turn out more physicians, nurses and medical technologists at a time when potential students were more attracted to nonmedical degrees. Again, more room was needed. "We now are training 92 entering medical students in the space designed for 72," he noted. Things improved with construction of the seven-story Basic Science Building in 1972. Today it houses School of Medicine student classrooms, laboratories and offices. Also in 1972, a nine-story wing was added to the teaching hospital to house modern surgical and therapeutic radiologic facilities.

New clinical programs were also instituted under Dean Holman's leadership: a residency in family practice, a prenatal emergency transport system, the Oregon Eye Bank, the Oregon Kidney Donor Program and the Rosenfeld Center for the Study and Treatment of Child Abuse. Outpatient services were expanded to include dozens of general and specialty clinics in such fields as dermatology, family medicine, pediatrics, obstetrics and gynecology, ophthalmology and psychiatry. Today about 135,000 outpatient visits and 22,000 emergency visits are recorded each year.

The years 1973-1974 brought major changes to the campus on Marquam Hill. In 1973, the School of Medicine acquired the county hospital, renaming it University Hospital north; the Medical School Teaching Hospital became University Hospital south.

In 1974, the University of Oregon Health Sciences Center was "founded." The medical school, along with the schools of dentistry and nursing, University Hospital, University Clinics and the Crippled Children's Division, became one free-standing institution totally independent of the University of Oregon (Figure 8). This independence was clarified in 1981 when the health center was renamed the Oregon Health Sciences University.

The first president of the new health center was Lewis W. Bluemle, Jr, MD, who had been president of Upstate Medical Center, State University of New York. Along with the institution's status as a health sciences center came the

Figure 9.—The photograph shows an aerial view of the Oregon Health Sciences University campus in 1986. The crane in the left corner depicts early construction of the Vollum Institute for Advanced Biomedical Research.

authority—previously held by the University of Oregon—to grant degrees to its students.

Guiding the medical school through this period of transition was Dr Robert Stone, a pathologist and graduate of the State University of New York College of Medicine in Brooklyn. Dr Stone was the first dean to be appointed from outside the ranks of the medical school faculty.

Dr Stone was succeeded in 1979 by Ransom Arthur, MD, who is credited with preserving the quality of the medical school program during a period of fiscal constraints. Dean Arthur, a psychiatrist and graduate cum laude from Harvard Medical School, was a strong promoter of research programs and was responsible for attracting several young medical investigators to the university. Since his departure in 1982, Arthur has been remembered by colleagues as a problem-solver and as a man of patience and understanding who had the ability to counsel department chairs and faculty members.

Leading the School of Medicine into its second hundred years is John Kendall, MD. Appointed dean in 1983, Kendall earned his medical degree at the University of Washington School of Medicine, Seattle, has worked extensively in neuroendocrinology and has established a national reputation in academic medicine over the past two decades.

As a former administrator at the Veterans Administration (VA) Medical Center, Dean Kendall is credited with building the Portland VA's research program into one of the major national centers of the VA research system. Under his leadership, the Portland VA increased its annual federal research support from $100,000 to $2 million in areas such as cell biology, immunology, molecular oncology, regeneration and health services research.

The year of Dean Kendall's appointment coincided with the arrival on the hill of the Shriners' Hospital for Crippled Children. Built adjacent to University Hospital north, the 39-bed facility serves as a teaching and research affiliate for the School of Medicine. And currently under way is a multimillion-dollar renovation of hospital facilities and construction of a new 420-space parking structure.

The Next Hundred Years

As a vital component of the OHSU, the School of Medicine is benefiting from the many new developments on Marquam Hill that are taking shape under the leadership of Dr Leonard Laster, OHSU president. Dr Laster came to the OHSU in 1978 with a new vision—one calling for new centers of excellence, a "critical mass" of researchers and health care professionals and a growing partnership of public and private support.

Today his vision is becoming a reality. For example, the Vollum Institute for Advanced Biomedical Research, completed this year, is applying molecular biology to the study of the brain and nervous system. Its 86,000 square feet distributed over five stories (Figure 9) provides an environment for the exchange of ideas and creative research among the scientists and staff who are working there. The institute has attracted scientists from the Massachusetts Institute of Technology, Yale, Stanford, Harvard, Columbia and other leading universities.

To keep pace with the rapid flow of information, the Biomedical Information and Communications Center, now in the planning stage, will serve as a model information center by using the latest technology to quickly bring vital medical data and information to health care professionals throughout the state.

Also in the planning stages is an $18.5 million regional eye center where basic scientists and clinicians in ophthalmology will work closely in developing new techniques to prevent and treat diseases of the eye. The recently funded Center for Occupational Disease Research is the only one of its kind in the United States that will use molecular biology to investigate damage to the nervous system caused by exposure to toxins in the workplace. The Oregon Hearing Research Center was recently funded with a $4.7 million federal appropriation; and, in the future, the OHSU hopes to create a center for the study of aging and a center for the application of advanced biomedical technology to clinical practice.

The philosopher Thomas Carlyle once wrote, "Nothing that was worthy in the past departs." What was worthy in the OHSU School of Medicine's past remains with us in this centennial year: a steadfast commitment to excellence, quality and compassion in the healing arts.

Commentary

Genetic Markers in Huntington's Disease

ELLIOT M. FROHMAN, *Irvine, and* JOSEPH B. MARTIN, MD, PhD, *Boston*

Huntington's disease is a neurodegenerative disorder that is inherited as an autosomal dominant trait. It is typically expressed later in a patient's adult years, when it may have already been transmitted to the patient's children. The clinical symptoms of this disorder include a progressive dementia combined with extrapyramidal motor manifestations of the choreoathetotic type. Huntington's disease has as its most prominent neuropathologic feature a notable atrophy of the caudate nucleus, which is accompanied by less severe degeneration in the putamen, globus pallidus and the cerebral cortex. Studies have shown that patients with Huntington's disease have alterations in striatal receptors for γ-aminobutyric acid (GABA), benzodiazepines, muscarinic cholinergics, cholecystokinin and dopamine. Such changes have been related to some extent to the loss of local circuit cholinergic and GABAergic neurons as well as those neurons that project from the striatum to other portions of the basal ganglia. A reduction in feedback inhibition of dopaminergic cells in the substantia nigra may lead to augmented dopaminergic activity in the striatum, a putative precondition in the development of the choreoathetosis characteristic of the disease.

Recently, a DNA sequence probe called G8 has been identified and has been shown to be closely linked to the Huntington's disease gene on chromosome 4. This new marker is a 17.6-kilobase fragment of DNA that after digestion with the bacterial restriction enzyme, Hind III, can give rise to one of four fragments or polymorphisms. These haplotypes are called A, B, C and D. The discovery of the localization of a restriction fragment length polymorphism linked to the Huntington's disease gene constitutes the first use of recombinant DNA technology to locate a gene without having any previous knowledge regarding gene location.

The use of this marker for the purpose of prediction tests in persons at risk represents a great advance in our ability to unmask the predisposition to a complex hereditary disease. Unfortunately, in the use of the G8 marker, the sequence is not close enough to the gene so that one haplotype invariably segregates with the presence of Huntington's disease. For this reason an error rate due to genetic recombination of 5% to 10% occurs even when a sufficient number of family members is available for study. Ideally, both the grandparents and parents of a person at risk should be available for analysis of the G8 marker. An additional caveat in the use of this marker for prediction testing in Huntington's disease is that the onset of the disorder is late enough in life that some of the parents and grandparents will probably be deceased.

The use of prediction testing involves two principal components: marker identification and pedigree analysis. In the most elementary and informative case, information is available from three generations: the grandparents, the parents and the person at risk. Prediction is more difficult when information from only two generations is available. An additional confounder in the prediction test is the possible error caused by recombination between the marker and the locus of the Huntington's disease gene.

An example of the process of genetic analysis will illustrate the use of the probe. In the best of circumstances wherein the grandparents and parents are alive, an affected parent might have received the Huntington's disease gene and the A marker haplotype from one of the affected grandparents, the other grandparent and parent being unaffected and labeled BB and CC, respectively. If the child also received an A marker, then in the absence of recombination this person at risk would be expected to be affected and hence labeled AC or AB. If the person at risk were BC, then, also barring the possibility of recombination, this person would be expected to be normal. It is important to point out that the A, B, C, D haplotypes represent only labels for polymorphism. Any one family may have associated with it any of the four labels. Moreover, the significance of such polymorphisms in the marking of the disease state concerns the presence of one of these haplotypes in conjunction with the affected person. It then becomes likely that, barring errors of recombination, offspring with the disease-associated haplotype will be afflicted with the disease.

At present additional markers are being generated to flank and, ultimately, converge on the Huntington's disease gene itself. The addition of these new markers serves to increase heterozygosity and thereby provide more precise counseling because a greater pattern complexity allows us to better distinguish between persons.

The development of a testing procedure for a disease that is lethal, of late onset and for which there is no current treatment is not without significant controversy. For instance, there is speculation that in those who test positive there will be an escalated risk of suicide, psychiatric manifestations, substance abuse, divorce and employment problems, to name just a few. The development of these testing procedures, however, will begin to assume greater importance when the prospects of early diagnosis will contribute to optimizing the potency of forthcoming treatment stratagems. In essence, these new findings represent a major advance toward the progression of steps that will lead to the understanding, treatment and prevention of hereditary disorders such as Huntington's disease. Finally, despite the considerable limitations of the current testing procedures, there is confidence that over the next five to ten years, gene isolation techniques will become available so that all suspected persons can be tested regardless of which relatives are available for pedigree analysis.

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From the 4th Year MD/PhD Program, Departments of Neurology, Anatomy and Neurobiology, University of California, Irvine, California College of Medicine (Mr Frohman), and the Neurology Service, Massachusetts General Hospital, Harvard Medical School, Boston (Dr Martin).

At the time this article was written, Mr Frohman was a student representative on the California Medical Association's Advisory Panel on Neurology.

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Health Care Delivery

Does a Helicopter Service Stimulate Financially Motivated Transfers?

KENNETH J. RHEE, MD; ROBERT J. O'MALLEY, RN; JAMES E. TURNER, MD; NEIL H. WILLITS, PhD, *and* RICHARD E. WARD, MD, *Sacramento, California*

Injured patients transferred to a trauma center from emergency departments and inpatient hospital units by a new helicopter transport service were studied to determine if this new service stimulated financially motivated transfers.

(Rhee KJ, O'Malley RJ, Turner JE, et al: Does a helicopter service stimulate financially motivated transfers? West J Med 1987 Oct; 147:487-488)

The initiation of a hospital-based helicopter service may increase the number of patients transferred to a trauma center both from within the local area and from a greater distance away.[1] During the planning of a helicopter service at University Medical Center (UMC), Sacramento, California, hospital administrators expressed concern that the new service might be used to selectively transfer patients who would be unable to pay for their care, a practice sometimes referred to as dumping.[2] To address these concerns, a study was initiated to determine whether helicopter transport increased financially motivated transfers from community hospitals. It was anticipated that most patients would be victims of trauma and, therefore, this group was selected for investigation.

Patients and Methods

All trauma patients transported to UMC from an emergency department or hospital inpatient service by helicopter during the first year of operation were studied. Patients were either admitted to the trauma, neurosurgical or orthopedic services or were discharged from the emergency department. Burn service patients were excluded because a stable referral pattern based on explicit indications for transfer existed.

UMC is the trauma center for the County of Sacramento and is a regional referral source for a large part of northern California and the Central Valley. During the study period no trauma patients were refused transfer.

Two of us, one the chief flight nurse (R.J.O.) and one a physician (K.J.R.), classified the patients into one of two groups: those whose transfer was helicopter-dependent—that is, because of the new helicopter service; and those whose transfer was independent of the helicopter service. This classification was done without knowledge of the charges or collections, and simple decision criteria were used (shown in Figure 1). Patients were first divided into two groups: patients who likely would have been transferred to UMC based on previous referral patterns (old referrals); and patients who previously would not have been transferred to UMC (new referrals). In marginal cases the patient transfer was considered an old referral. Old referrals were considered helicopter-dependent only if the clinical situation would have precluded transfer by any other means, such as the transfer of a patient directly from an operating room. New referrals were considered helicopter-dependent unless it appeared that the helicopter service played no significant role in the decision to transfer the patient, such as a helicopter being used rather than a ground transport on the suggestion of a UMC physician.

Total charges, including both hospital and helicopter charges, and total collections were abstracted from the hospital information system. All accounts had been active for more than eight months. χ^2 Analysis was used to test for dependence between categoric variables and referral type. This included the location of pickup (emergency department or inpatient unit), type of insurance (government sponsored, private insurance, no insurance, contracted services) and diagnostic group (multiple trauma, primarily neurosurgical injury, spinal cord injury, primarily orthopedic injury). The Trauma Score,[3] total charges, total collections and the collection:charge ratio were compared using both analysis of variance and the Kruskal-Wallis test. In all cases statistical significance was chosen to be $< .05$.

Results

A total of 98 injured patients was transferred by helicopter from emergency departments or inpatient hospital services to UMC during the study period. Of these, 57 patients (58%) were classified as helicopter-independent and 41 (42%) as helicopter-dependent. A total of 79 of the patients (81%) were transferred from an emergency department and 19 (19%) from an inpatient hospital service. A frequency diagram of patients by diagnostic groups and insurance carrier is given in Table 1. The helicopter-independent and -dependent groups were not significantly different with regard to location of pickup, diagnostic group or type of insurance.

The average Trauma Score on arrival at UMC was 13.4 for both the helicopter-independent and the helicopter-dependent patients. The average age was 28 years for the helicopter-independent patients and 30 years for the helicopter-dependent patients. For the helicopter-independent group, the average hospital bill was $34,360, the average collection was

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Reprint requests to Kenneth Rhee, MD, Division of Emergency Medicine, Trailer 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

$26,174 and the ratio of collections to charges was 0.760. For the helicopter-dependent group the average hospital bill was $30,199, the average collection was $23,907 and the ratio of collections to charges was 0.794 (Table 1). The ratio of collections to charges was 0.768 for emergency department transfers and 0.799 for inpatient transfers. These two groups were not significantly different in any of the variables using either a one-way analysis of variances or a Kruskal-Wallis test.

Discussion

Initiating a helicopter emergency medical service is an expensive undertaking for any hospital because of both the direct costs of the program and the indirect costs to the hospital in terms of the additional resources required to care for the patients brought to the hospital by helicopter. Recent evidence from California suggests that the care of motor-vehicle accident victims is a break-even proposition with a percentage collection of 80.3%.[4] Several reports in the medical literature have voiced concerns about financially motivated transfers.[5-7] These reports raise legitimate fears that a new aeromedical service might be used to selectively transfer patients not able to pay for the costs of their care.

To study this issue one might simply ask referring physicians whether financial factors influenced their decision to transfer a patient. Even if complete honesty could be relied on, however, the actual weighing of factors that produced the referral would be impossible to quantify in a consistent manner. We chose instead to compare a control group—helicopter-independent patients—with a group of patients thought to be transferred because of the new aeromedical service—helicopter-dependent patients. Both groups comprised a similar proportion of multiple trauma and head-injured patients whose severity of injury was significant and similar. A Trauma Score[3] was used to control for case-mix severity because it is widely accepted, extensively validated and sensitive to the physiologic state of the patient. An indirect measure of severity of injury, the hospital resources required to care for patients as measured by the total hospital charges, was similar as well. Measures of potential and actual payment, insurance type, total collections and the ratio of collections to charges were not significantly different. The similar clinical and financial profiles of the two groups suggest that patients thought to be transferred because of the new aeromedical service were referred for similar reasons as for the control group. We therefore concluded that the aeromedical service did not stimulate financially motivated transfers.

TABLE 1.—*Helicopter-Transferred Patients, by Diagnostic Group and Type of Insurance*

	Helicopter-independent N = 57	*Helicopter-dependent* N = 41
Diagnostic Groups		
Multiple trauma	26	23
Neurosurgical	25	14
Spinal cord	3	1
Orthopedic	3	3
Type of Insurance		
Government	16	11
Private	28	26
No insurance	5	2
Contract	8	2
Clinical Information		
Trauma Score*	13.4	13.4
Age, years*	28	30
Financial Profile		
Charges*	$34,360	$30,199
Collections*	$26,174	$23,907
Charges/collections*	0.760	0.794

*Numbers represent average for the group No statistically significant difference between groups.

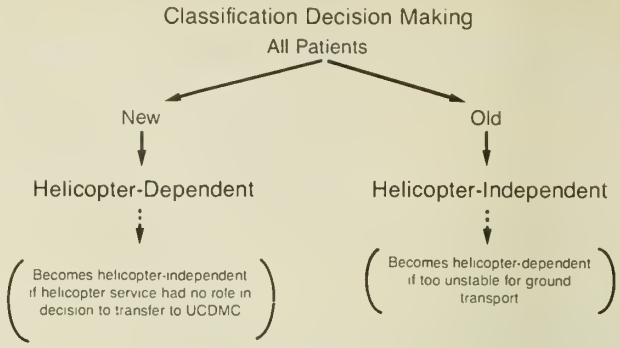

Figure 1.—The method of classifying patients into helicopter-dependent and helicopter-independent groups.

This information might be viewed from two different perspectives. From a hospital administrator's point of view, the main question to be answered is what the financial impact of helicopter-dependent patients is on the hospital. Analysis of variance addresses this question. At UMC, helicopter-dependent patients paid a higher percentage of charges than did helicopter-independent patients, although this did not reach statistical significance. One or two patients with very large bills could dramatically change this picture.

From the point of view of a policymaker, the question to be answered is whether physicians systematically transfer patients based on ability to pay. This did not seem to occur in the new UMC referral network. The type of insurance coverage was similar in the helicopter-dependent and -independent groups, suggesting that there was no intent to transfer underinsured patients selectively. Furthermore, analyses of charges, collections and individual collection:charge ratios using the Kruskal-Wallis test suggest no differences between the helicopter-independent and -dependent groups. The Kruskal-Wallis test is a nonparametric method of analysis in which the rank order rather than the specific numeric values is analyzed. In this study, the distribution of patients in the two groups was compared after placing them in rank order based on the monetary values. The Kruskal-Wallis method does not assume that populations possess a normal probability distribution or that the variances are equal. Overall trends are revealed and the impact of very large or very small values is reduced.

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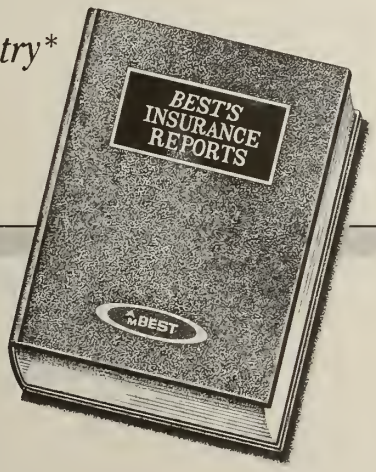

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CONTINUING MEDICAL EDUCATION

(Continued from Page 416)

January 31-February 5—**Biennial Western Conference on Anesthesiology: 1988 Clinical Update in Anesthesiology.** Toussaint Hospital Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. 22.5 hrs. $375. Contact: Murray G. Atnikov, c/o Box F110-63, Baline, WA 98230. (604) 874-5291.

October 18-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Westin Maui, Kaanapali Beach, Hawaii. Sun-Fri. 20 hrs. $375. Contact: California Society of Anesthesiology, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

CANCER

October 19-21—**11th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 21 hrs. $350. Contact: Nomi Feldman, Scripps Memorial Hospital, 3770 Tansy, San Diego 92121. (619) 453-6222.

October 23—**The Impact of Unproven Cancer Treatment on Oncology Practice Today.** American Cancer Society at Clarion Hotel, Sacramento. Fri. 6 hrs. Contact: Cecelia Olkowski, American Cancer Society, California Division, PO Box 2061, Oakland 94604. (415) 893-7900.

October 29-30—**Update on Common Cancer for the Primary Care Physician: Breast, Colon and Prostate.** UCSF. Thurs-Fri. 12 hrs. Contact: UCSF.

November 6—**Managing Breast Cancer.** Sutter Community Hospitals at Red Lion Inn, Sacramento. Fri. 7 hrs. $75. Contact: Sutter Community Hospital, CME Dept. 2020 I St, Ste D, Sacramento 95814. (916) 446-7681.

December 3-5—**Recent Advances in Occupational Cancer.** Northern California Occupational Health Center and UCSF at Miyako Hotel, San Francisco. Thurs.-Sat. $220. Contact: UCSF.

December 9—**23rd Northern California Cancer Conference.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th and The Esplanade, Chico 95926. (916) 891-7300.

December 12—**Bronchology Laser Cancer Symposium.** UCI at Long Beach. Sat. Contact: UCI.

February 4-6—**Third International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. 19 hrs. $310. Contact: UCSD.

February 25-27—**Second International Conference on Intracavitary Chemotherapy.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 18 hrs. $300. Contact: UCSD.

CARDIOLOGY

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 30-31—**Coronary Heart Disease.** Medical Education Resources at Las Vegas Hilton Hotel, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 13-14—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hilton Hotel, San Francisco. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

November 14—**16th Annual Cardiology Symposium.** Fresno Community Hospital at Center Plaza Hotel, Fresno. Sat. Contact: Joann Ellis, Fresno Community Hospital, PO Box 1232, Fresno 93715. (209) 442-3936.

December 3-4—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Beach Marriott, Newport Beach. Thurs-Fri. Contact: UCI.

December 4-5—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

January 22-24—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 28-30—**Clinical Nuclear Cardiology.** ACC at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 11-13—**Second Annual International Symposium: Clinical Strategies in Complex Valvular Heart Disease.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 16 hrs. $350. Contact: UCSD.

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

DERMATOLOGY

October 24-25—**16th Annual Mycology Review.** STAN at STAN. Sat-Sun. Contact: STAN.

EMERGENCY MEDICINE

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

October 26-30—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550.

October 29-November 1—**Traumatic Brain Injury 1987: A Meeting of the Minds-Science and the Injured Brain.** UCD at Red Lion Motor Inn, Sacramento. Thurs-Sun. 30 hrs. $395. Contact: UCD.

May 11-15—**Tenth Annual Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith S. Bookstein/WMW, PO Box 1386, La Jolla 92038. (619) 454-3212.

INTERNAL MEDICINE

October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 28—**Endocrinology Ninth Annual Symposium**-Hospital of the Good Samaritan at Moseley-Salvatori Conference Center. Wed. 5.5 hrs. $90. Contact: Mary Anne Clark, 616 South Witmer St, Los Angeles 90017. (213) 977-2335.

November 11—**Gastroenterology.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

November 14—**Recent Advances in Diagnosis, Management, and Prevention of Deep Vein Thrombosis and Pulmonary Embolism.** UCD at Sacramento Inn. Sat. $95. Contact: UCD.

December 20-24—**Immunology, Rheumatology and Allergy.** Symposium Maui at Royal Lahaina Resort, Maui. Sun-Thurs. 18 hrs. $395. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 1-4—**Specialties and Primary Practice.** Symposium Maui at Royal Lahaina Resort, Maui. Fri-Mon. 13.5 hrs. $295. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 19-23—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton, Beverly Hills. Tues-Sat. 40 hrs. Contact: UCLA.

February 15-17—**Clinical Hematology and Oncology: 1988.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 7-12—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Incline Village. Sun-Fri. 18.5 hrs. $365. Contact: UCSF.

March 4-5—**Gastrointestinal Endoscopy 1988.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Fri-Sat. Contact: David S. Cantor, MD, 50 Alessandro, Ste 410, Pasadena 91105. (818) 793-7114.

(Continued on Page 491)

CONTINUING MEDICAL EDUCATION

(Continued from Page 490)

March 11-17—**Internal Medicine 1988: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Fri-Thurs. 54 hrs. $495. Contact: Jackie Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

October 16-18—**Advanced Fetal Heart Rate Monitoring.** UCI at Embassy Suites Hotel, Napa Valley. Fri-Sun. Contact: UCI.

November 15-21—**10th Annual Review Course in Clinical Obstetrics & Gynecology and/or Gynecological Histopathology** at UCI. Sun-Sat. Contact: UCI.

November 16-20—**18th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

December 4-5—**Environmental Exposure and Fetal Development (March of Dimes).** UCD at Sacramento Inn. Fri-Sat. Contact: UCD.

January 18-22—**19th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

February 7-11—**16th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki. Sun-Thurs. Contact: Ohio State University, 410 W 10th Ave, Columbus, Ohio 43210. (614) 293-8487.

February 11-14—**43rd Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: Director of Medical Education, OB-GYN Assembly of California, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

OPHTHALMOLOGY

October 17—**Glaucoma 1987: Medical and Surgical Management of Secondary Glaucoma.** National Society to Prevent Blindness and Estelle Doheny Eye Institute at Le Meridien Hotel, Newport Beach. Sat. 7 hrs. $175. Contact: Daniel J. Sigband, MD, National Society to Prevent Blindness, 249 E Emerson Ave, Ste F, Orange 92665. (714) 974-EYES.

December 10-11—**Ophthalmic Plastic and Reconstructive Surgery: Past, Present, and Future—A Tribute to Crowell Beard, MD.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Fri. 12 hrs. $325. Contact: UCSF.

PATHOLOGY

November 10—**Surgical Pathology: 1987.** UCSF. Thurs. $30. Contact: UCSF.

December 8—**Surgical Pathology: 1987.** UCSF. Tues. $30. Contact: UCSF.

PEDIATRICS

October 16-17—**2nd Annual Symposium on Advanced Pediatric Emergency Medicine and Trauma.** UCI at Long Beach Airport Marriott Hotel. Fri-Sat. Contact: UCI.

October 16-18—**Current Advances in Pediatrics.** American Academy of Pediatrics and UCI at Disneyland Hotel, Anaheim. Fri-Sun. Contact: AAP, PO Box 1297, Orange 92668. (714) 978-2415.

October 23-25—**Current Concepts in Pediatric Gastroenterology.** Children's Hospital, Oakland at Doubletree Hotel, Monerey. Fri-Sun. Contact: Kim Leadon, CME Office, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

(Continued on Page 492)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 491)

October 24—**Cardiology.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 24—**Endocrine/Metabolic.** Los Angeles Pediatric Society at UCLA. Sat. 6.5 hrs. $275. Contact: LAPS, PO Box 2022, Inglewood 90305. (213) 757-1198.

November 20-23—**9th Annual Las Vegas Seminars—Pediatric Update.** Los Angeles Pediatric Society at Caesar's Palace. Fri-Mon. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 4-6—**Current Concepts in Pediatric Medicine—1988.** Childrens Hospital and Health Center, San Diego at Holiday Inn, Embarcadero, San Diego. Thurs-Sat. Contact: Children's Hospital San Diego. 8001 Frost St, San Diego 92123. (619) 576-1700.

February 20-27—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Royal Lahaina Resort, Maui. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

PSYCHIATRY

October 17-18—**Dynamics of Human Development—Implications for Treatment.** Continuing Education Seminars at Los Angeles. Sat-Sun. 11.5 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave, Los Angeles 90024. (213) 475-8300.

November 6-8—**33rd Annual: Group Therapy Symposium.** UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sun. Contact: UCSF.

November 7-8—**The Resistant Patient: Differing Perspectives of Classical Psychoanalysis and Self-Psychology.** San Diego Psychoanalytic Society and Psychonanalytic Institute at San Diego. Sat-Sun. Contact: San Diego Psychoanalytic Institute, 1010 Turquoise St, Ste 320, San Diego 92109. (619) 488-0687.

November 30-December 1—**Behavioral Science as an Approach to Accident Prevention.** USC. Mon-Tues. 1.4 hrs. $375. Contact: USC.

January 21-24—**Health Science Response to Child Maltreatment—1988.** Children's Hospital and Health Center ar Hanalei Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Children's Hospital and Health Center, 8001 Frost St, San Diego 92123. (619) 576-1700.

March 27-31—**Adapting to Social Change, Therapy, Technology and Services.** American Orthopsychiatric Association at Hilton Square, San Francisco. Sun-Thurs. Contact: ORTHO, 19 W 44th St, #1616, New York, NY 10036. (212) 354-5770.

RADIOLOGY

October 17-18—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. Contact: UCSF.

October 19-23—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. $495. Contact: UCSF.

October 19-23—**12th Annual San Diego Postgraduate Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 28 hrs. $425. Contact: Dawne Ryals, POBox 920113, Norcross, GA 30092-0113. (404) 641-9773.

November 2-6—**Diagnostic Radiology Seminars.** UCSF at Westin Hotel, Hawaii. Mon-Fri. 22.5 hrs. $495. Contact: UCSF.

January 21-23—**Duplex Imaging.** UCSD at Inter-Continental Hotel, San Diego. Thurs-Sat. 18 hrs. $375. Contact: UCSD.

January 24-31—**Radiology for Emergency & Primary Care Physicians.** American Institute of Postgraduate Education and Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Kona, Hawaii. One Week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 3586, La Jolla 92038. (619) 454-3212.

January 29-31—**Fortieth Annual Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20hrs. $250. Contact: Los Angeles Radiological Society-MWOC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

February 2-6—**14th Annual Post Conference Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Tues-Sat. 18 hrs. $375. Contact: Los Angeles Radiological Society-MWRC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

SURGERY

October 17-18—**Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at San Francisco. Sat-Sun. 12 hrs. Contact: Terri Harrington, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 18-24—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 14-15—**Automated Percutaneous Discectomy Workshop.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. 8 hrs. Contact: UCSF.

November 21—**Primary Care Course.** American Society for Surgery of the Hand at Los Angeles. Sat. 7 hrs. Contact: Anne Turner, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

December 6-12—**Temporal Bone Surgical Dissection—1987.** House Ear Institute at House Ear Institute, Los Angeles. Sun-Sat. 62 hours. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 10-15—**Temporal Bone Surgical Dissection Courses—1988.** House Ear Institute. Sun-Fri. 62 hrs. Contact: House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

October 16-18—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $365. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-22—**Annual Family Practice Update.** Mon-Thurs. LLU at LLU. Contact: LLU.

October 19-30—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI at Long Beach. Mon-Fri. Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

October 22-24—**West Coast Counties Postgraduate Institute.** California Medical Association at Sheraton Hotel, Monterey. Thurs-Sat. 12 hrs. Contact: Janice Rigney, CMA, PO Box 7690, San Francisco 94120-7690. (415) 863-5522, ext. 416.

October 24-31—**Ninth International Seminar on Operative Arthroscopy.** UCLA at Marriott Resort Hotel, Maui. One week. 30-36 hrs. $850. Contact: UCLA.

October 26-30—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 26-November 1—**Traumatic Brain Injury.** UCD at Red Lion Motor Inn, Sacramento. Mon-Sun. Contact: UCD.

November 2-6—**Sampling and Evaluating Airborne Asbestos Dust.** USC. Mon-Fri. 3.5 hrs. $725. Contact: USC.

November 10-13—**Industrial Ventilation Fundamentals.** USC at USC Study Center, San Diego. Tues-Fri. 2.8 hrs. $675. Contact: USC.

November 12-14—**2nd Annual: Progress in Impotence—Workshops/Seminars.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. 13 hrs. $295. Contact: Edith Bookstein/UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 18—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wed. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service, (117) VAMC, 16111 Plummer St, Sepulveda 91343. (818) 891-2473.

November 22—**Controversy in Modern Medicine—1987.** Granada Hills Community Hospital and UCLA at Sheraton Universal Hotel, N Hollywood. Sun. 7 hrs. $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021.

December 7-18—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

(Continued on Page 493)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 492)

February 2-4—**11th Annual: Neurology for Non-Neurologists.** UCSD and Neurology for Non-Neurologists Foundation at Holiday Inn Embarcadero, San Diego. Tues-Thurs. 21 hrs. $395. Contact: Edith S. Bookstein/NNN, PO Box 3586, La Jolla 92038. (619) 454-3212.

February 3-5—**Clinical Laboratory Molecular Analysis: Future Perspectives.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 24 hrs. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines, Rd, La Jolla 92037. (619) 457-8556.

February 11-13—**21st Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

February 13-15—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs. Sat-Mon. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262. (619) 325-5588.

February 19-21—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs at Desert Hospital. Fri-Sun. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262.

March 18-19—**Hematology: Neonatal, Pediatric and AIDS Related Issues.** Children's Hospital, Oakland at Berkeley Marina Marriott Hotel. Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Department, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

March 26-April 2—**Orthopedic Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Waiohai and Poipu Beach Hotels, Kauai. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 13-17—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Desert Princess Resort, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

MONTANA

February 18-20—**7th Annual Big Sky Pulmonary Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Thurs-Sat. Contact: ALA of Montana, 825 Helena Ave, Helena 59601. (406) 442-6556 or 1 (800) 252-6368 (in Montana).

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 7-December 1—**History of Medicine Seminar—Prehistory to the Eighteenth Century.** David A. Bennahum, MD, Instructor. Medical Center Library, University of New Mexico, Albuquerque. 4-6 pm, Tuesdays.

(Continued on Page 494)

CONTINUING MEDICAL EDUCATION

(Continued from Page 493)

October 23—**Update in Cardiology.** Albuquerque. Fri. Contact: Charles Karaian, MD, 1101 Medical Arts Ave NE, Albuquerque 87102. (505) 842-8321.

October 23-25—**The 12 Lead ECG for the Primary Care Physician.** Presbyterian Hospital, Albuquerque. Fri-Sun. Contact: The Presbyterian Heart Institute, Barry W. Ramo, MD, (505) 242-2796.

November 13-14—**New Mexico Medical Society Interim Meeting—Risk Management.** Sally Port Inn, Roswell. Fri-Sat. Contact: NMMS, (505) 266-7868.

December 3-5—**American College of Physicians, New Mexico Chapter—Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

December 11-12—**Trauma Update '87.** UNM Conference Center, Albuquerque. Fri-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

January 5-March 1—**History of Medicine Seminar—Modern Medicine.** David A. Bennahum, MD, Instructor. Medical Center Library, University of New Mexico, Albuquerque. 4-6 pm, Tuesdays.

February 25-27—**Santa Fe Ski Symposium—Hypertension—1988.** Santa Fe. Thurs-Sat. Contact: National Kidney Foundation of New Mexico, 1715 Girard, NE, Albuquerque 87106. (505) 266-4573.

February 26-28—**16th Annual Thoracic Society Lung Disease Symposium.** Santa Fe Hilton. Fri-Sun. Contact: Lung Association, (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 8-13—**Utah Ophthalmological Society Annual Winter Meeting** (Sponsor: UOS). Mon-Sat. Little America Hotel, Salt Lake City. 15 hrs. Contact: Carol Leavitt, (801) 355-7477.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 15-17—**Annual Review of Neurosurgery.** Seattle. Thurs-Sat. Contact: U/W.

October 16—**Psychosis: What's New, What's True.** Seattle. Fri. Contact: U/W.

October 16—**21st Annual Cancer Conference: Breast Cancer—Issues Faced by the Primary Care Physician & Patient.** Seattle. Fri. Contact: VMMC.

October 17—**Plastic Surgery Education Foundation Teleconference: Eye Surgery.** Spokane. Sat. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

October 29—**AHA Teleconference: Ambulatory Care and Emergency Services.** Spokane. Thurs. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

October 29-31—**Orthopedic Review.** Seattle. Thus-Sat. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

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(Continued on Page 503)

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IN HYPERTENSION

resistance in the elderly[1]

- Effective blood pressure control
- Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]

Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia

See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.

TRANDATE® *b.i.d.*

labetalol HCl/Glaxo *100 mg/200 mg tablets*

Because it also vasodilates

References: 1. Holtzman JL, Finley D, Johnson B, et al: The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. 2. Due DL, Giguere GC, Plachetka JR: Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. 3. Burns JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9. 4. Erb RJ, Plachetka JR: Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.

Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.

Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

Cardiovascular: Edema and postural hypotension.

Respiratory: Dyspnea.

Skin: Rash.

Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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September 1986

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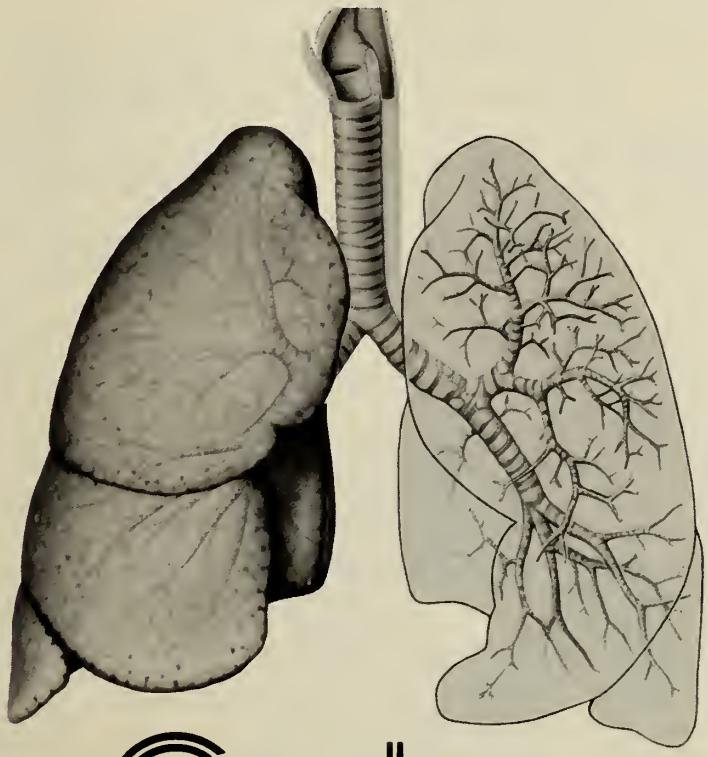

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cefaclor

250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae, Streptococcus pneumoniae
(ampicillin-susceptible and ampicillin-resistant)

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).

Contraindication:
Known allergy to cephalosporins.

Warnings:
CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever): 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

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(Continued on Page 502)

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(Continued from Page 500)

PHYSICIANS WANTED

CARDIOLOGIST, INVASIVE. 160-physician, multispecialty, prepaid group located in the San Francisco bay area wishes to add another Cardiologist/Internist. Practice includes large volume of referrals for invasive procedures. Doppler-echo skills required. University affiliation available. Please contact Larry Lawrence, MD, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119.

ONCE IN A LIFETIME OPPORTUNITY. Large general practice and clinic for sale by General Practitioner preparing for retirement. Practice is part of a progressive and rapidly expanding community located in central Minnesota near excellent winter and summer recreation. Current clinic grosses over $500,000 annually, is expandable and equipped with surgery, x-ray, lab and set up for pharmacy. Fee for service and growing! Malpractice insurance not a serious problem. Computerized; excellent staff. Great potential for aggressive GPs, FPs, Internists or Surgeons. Excellent hospital one mile. Contact Janet K. (612) 251-9191.

FULL-TIME POSITION Available now for Family Practice physician in Vancouver, Washington. Call Helen Mosier, (206) 256-4500.

NEPHROLOGIST/INTERNIST. Opening available in 160 plus physician group. Join additional Nephrologist/Internist in a busy and fulfilling HMO practice in the San Francisco bay area. Excellent working conditions. Ample opportunities for house staff teaching, clinical faculty appointment, cooperative group participation. Competitive salary. Superb benefit package. Reply with CV to Joseph Mason, MD, Chief, Department of Internal Medicine, The Permanente Medical Group, Inc, 260 International Circle, San Jose, CA 95119. An Equal Opportunity/Affirmative Action Employer.

INTERNAL MEDICINE—SAN FRANCISCO BAY AREA. Immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical house staff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, and retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Circle, San Jose, CA 95119.

FAMILY PRACTICE position available with 35-member multispecialty group; for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

EUGENE, OREGON. Well-established, eight-physician Family Practice group is seeking BC/BE Family Physician with interest in OB. Anticipate partnership after one year. Exceptional cultural and recreational opportunities. Home of University of Oregon. Please send CV to Rob Daugherty, MD, or Kendall Hills, MD, River Road Medical Group, 2400 River Rd, Eugene, OR 97404, or call (503) 688-7527.

OREGON COAST. General Internist and Family Practice including Obstetrics needed for busy Seaside multispecialty group. Well-equipped seven-year-old office next to 34-bed certified hospital with ICU/CCU unit. All BC group consists of three Family Practitioners, one Internist and two General Surgeons. Retirement/vacation area offers top-notch school system and excellent array of activities. Located just 75 easy miles from Portland adds even more cultural and shopping opportunities. Contact and/or send CV to Rick Bigger, North Coast Medical Center, PC, 727 Wahanna Rd, Seaside, OR 97138; (503) 738-9551.

PHYSICIANS WANTED

WASHINGTON STATE

Growing Puget Sound Community

Dominant multispecialty group of 14 to add:

ENT
PSYCHIATRIST
GENERAL SURGEON
ORTHOPEDIST
NEUROLOGIST
OB/GYN

Private practice option. Share expenses with well-structured group. Twenty minutes to 230-bed hospital. Female and male applicants encouraged. Young population, waterfront setting. One hour to Seattle.

The Friedrich Group, Inc.
9284 Fernclift Northeast
Bainbridge Island, WA 98110
(206) 547-7850 or (206) 842-5248

OTOLARYNGOLOGY position available with 35-member multispecialty group; for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

MONTANA. General Internal Medicine opportunity available immediately to associate with established, excellent Internal Medicine practice. ABIM necessary. Outdoorsman's paradise. Send CV to Ron Loge, MD, 401 Barrett, Dillon, MT 59725, or PROSEARCH, a division of Brim and Associates, 305 NE 102nd Ave, Portland, OR 97220-4199.

GASTROENTEROLOGIST WANTED. Solo GI practitioner with busy, established, downtown, teaching hospital practice looking for associate to start July 1988 or sooner. Must be BC/BE, endoscopically adept, and enjoy pacific northwest life-style. Send CV to Number 55, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PATHOLOGIST-AP-CP. To join three Pathologists, each of whom has subspecialty, in all new 18,000 square foot department. 300-bed hospital in northwest US. Work load requires fourth. Will be responsible for Micro and Infection Control, in addition to regular rotation. Preferably has advanced degree or fellowship in Microbiology. Competitive income, enviable climate with year 'round outdoor activities. Send CV with reply to Number 56, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ARIZONA. Emergency Medicine practice opportunities in the Phoenix metropolitan area. Active practice with double physician coverage; expanding group. Desirable location offering many outdoor recreational and cultural opportunities. Send CV to Ms Nancy Hayward, 1400 S. Dobson Rd, Mesa, AZ 85202 or call (602) 833-6180.

ONCOLOGIST, SAN FRANCISCO BAY AREA. Five-man group practice needs to replace retiring Oncologist. Practice includes Oncology and Internal Medicine. Position available July 1988. Send CV to Number 54, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

HOLBROOK, ARIZONA. A community of 7,000 only one and one-half hours from Flagstaff has an excellent opportunity for a BE Family Practitioner doing Obstetrics. Practice assistance includes first-year salary guarantee, free rent, and malpractice insurance. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070.

PHYSICIANS WANTED

INTERNAL MEDICINE position available with 35-member multispecialty group; for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

OB/GYN. Tulare County is looking for a BC/BE OB/GYN to practice in a outpatient clinic, which includes inpatient duties, with 14 physicians. The county provides a benefit package that includes malpractice insurance coverage. Consider a semi-rural life-style with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $98,112-$103,116 annually. Send CV to Tulare County Personnel, 2900 W. Burrel, Visalia, CA 93291; (209) 733-6266. Equal Opportunity Employer.

WASHINGTON. Openings for career oriented Emergency Physicians, BC/BE in Emergency or primary medical specialty. In a Seattle metropolitan hospital with 35,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 South 43rd St, Renton, WA 98055.

EMERGENCY MEDICINE. San Francisco bay area. BE/BC Emergency Physician for part-time, potential full-time, starting November 1, 1987 at Kaiser Hospital in San Rafael, and then joining new Santa Rosa Kaiser Hospital in 1988/1989. Competitive salary, outstanding benefits, AA/EOE employer. Contact John David, MD, Chief, Emergency Department, Kaiser San Rafael, 99 Montecillo Rd, San Rafael, CA 94903.

EXCELLENT TEXAS OPPORTUNITIES. ENT, Family Practitioner, General Practitioner, General Surgeon, Internal Medicine, OB/GYN, Ophthalmologist, Orthopedic Surgeon, Oncologist, Pediatrician and Vascular Surgeon to practice in one of several lake area communities, in the beautiful Piney Woods area of east Texas. Excellent quality of life, first year guarantee, etc. Other Texas opportunities available also. Reply with CV to Medical Support Services, Armando L. Frezza, 8806 Balcones Club Dr, Austin, TX 78750; (512) 331-4164.

INFECTIOUS DISEASE PHYSICIAN. Salary $2,424 bi-weekly. Full-time Infectious Disease physician required for large municipal geriatric and chronic care facility. Responsibilities include clinical consultation, infection control, teaching, and some general Internal Medicine. Requires BC in Internal Medicine and BE in Infectious Diseases. CVs will be accepted until there is a sufficient number of qualified applicants. Submit CVs immediately to Mary Anne Johnson, MD, Medical Director, Laguna Honda Hospital, 375 Laguna Honda Blvd, San Francisco, CA 94116; EOE: M/F/H.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

WORK PART-TIME. Position available for Internist or GP/FP with Internal Medicine experience in Primary Care Practice, northern California Sierra foothills community of 25,000. Share rotating practice with two other MDs; you work one week in three. Outpatient and inpatient responsibilities (no OB, no ICU) in modern, fully-equipped, 100-bed hospital. Minimum salary of $1,800/week (with incentives, actual will be around $2,200/week). Insurance, housing and meals provided N/C. Send CV to David Lomba, 133 'B' Ascot Ct, Moraga, CA 94556.

(Continued on Page 504)

CONTINUING MEDICAL EDUCATION

(Continued from Page 494)

November 5-6—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

November 6-7—**Cardiology Update.** Seattle. Fri-Sat. Contact: VMMC.

November 7—**Washington State Academy of Physician Assistants Conference: Dermatology.** Sat. Contact: Kory Diemert, (206) 441-9762.

November 12-13—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 13-14—**New Concepts in Laser Therapy: A Symposium.** Seattle. Fri-Sat. Contact: VMMC.

November 19—**AHA Teleconference: Ethics: Conflicts of Value, Challenge of Care.** Spokane. Thurs. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

November 20-21—**Innovations in Newborn Care: A Challenge for the 90s.** Seattle. Fri-Sat. Contact: NW Hospital, (206) 364-2229.

November 27-December 10—**Emergency and Critical Care Down-under.** Sites in New Zealand and Australia. Fri-Thurs. Contact: Washington Chapter, American College of Emergency Physicians, Georgine Elich, Kailani World Travel, 1 (800) 542-5264 or (206) 671-1800.

December 4-5—**Medico-Legal Aspects of Neurology.** Seattle. Fri-Sat. Contact: U/W, Alice Kuramoto, (206) 543-1047.

December 4-5—**Northwest Urological Society Annual Meeting.** Portland, Oregon. Fri-Sat. Contact: Pamela Moore, (206) 441-9762.

December 5—**Washington State Urology Society.** Portland, Oregon. Sat. Contact: Patti Smith, (206) 441-9762.

December 5—**Plastic Surgery Education Foundation Teleconference: Rhinoplasty.** Spokane. Sat. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

December 5—**Medico-Legal Aspects of Neurology.** Seattle. Sat. Contact: U/W.

December 5-6—**Washington State Society of Anesthesiologists—Winter Meeting.** Seattle. Sat-Sun. Contact: Patti Smith, (206) 441-9762.

December 10—**AHA Teleconference: Obstetrical Liability II: Excellence Under Fire.** Spokane. Thurs. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

December 11—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

January 20—**Health Effects of Wood Smoke.** Seattle. Wed. Contact: U/W, (206) 543-1069.

January 22—**Biliary Tract Diseases—Stones and Tumors.** Seattle. Fri. Contact: VMMC.

January 29-30—**Orbital Problems and Treatment: Plastic and Reconstructive Surgery (WSAO Annual Meeting).** Seattle. Fri-Sat. Contact: Patti Smith, (206) 441-9762.

February 4-5—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: U/W.

February 5—**Esophageal Disorders in Clinical Practice.** Seattle. Fri. Contact: VMMC.

February 10-13—**Washington State Academy of Physician Assistants CME Conference.** Bellevue. Wed-Sat. Contact: Kory Diemert, (206) 441-9762.

February 19-20—**Medicine for Psychotherapists.** Seattle. Fri-Sat. Contact: VMMC.

February 20-27—**Maternal-Fetal Medicine Update.** Seattle. One week. Contact: U/W.

March 3-4—**Northwest Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Thurs-Fri. Contact: William Lassey, (509) 747-1012.

March 4-5—**Soft Tissue Surgery.** Seattle. Fri-Sat. Contact: VMMC.

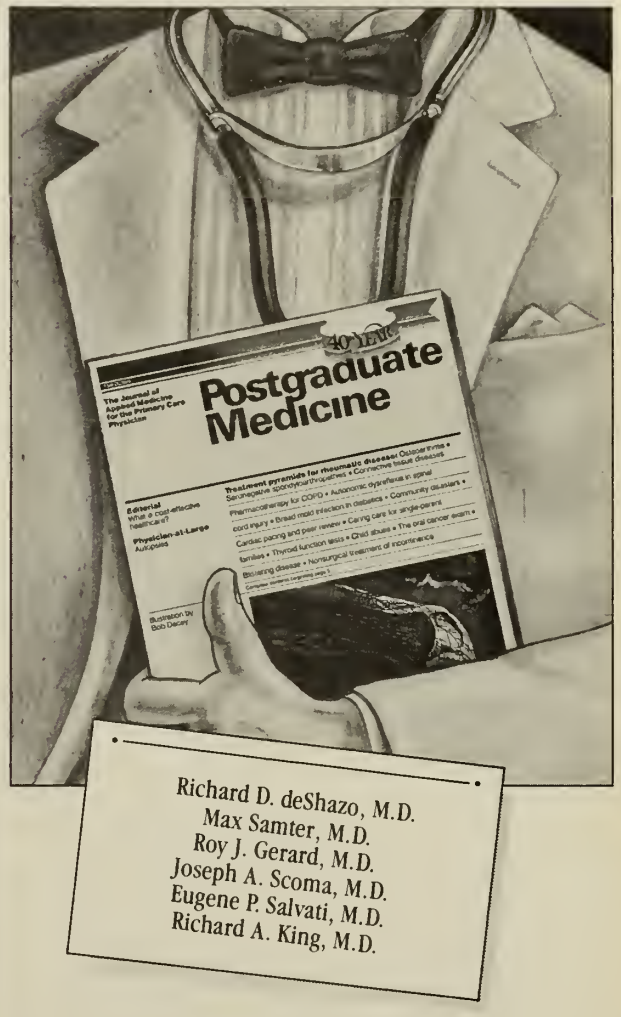
March 11—**Recent Developments in Occupational Medicine.** Fri. Contact: U/W, (206) 543-1069.

March 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

March 25—**Update in Contrast Media: An Evening of Uroradiology.** Seattle. Fri. Contact: VMMC.

March 23-25—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069. ◆

FAMOUS PHYSICIANS ARE SHOWING UP FOR OUR 40th YEAR CELEBRATION.



Read Every Issue From Cover to Cover:

October
Symposium: Allergy ..... Richard D. deShazo, M.D. Coordinator
Special Article: Allergy 1947-1987 ..... Max Samter, M.D.

November 1
Symposium: Focus on Family Practice ..... Roy J. Gerard, M.D. Coordinator

November 15
Symposium: Colon & Rectal Disease ..... Joseph A. Scoma, M.D. Coordinator
Special Article: Colon & Rectal Disease 1947-1987 ..... Eugene P. Salvati, M.D.

December
Symposium: Genetic Diseases
Special Article: Genetics 1947-1987 ..... Richard A. King, M.D.

40 YEAR
Postgraduate Medicine

Every Issue is a Celebration of Clinical Information

(Continued from Page 502)

PHYSICIANS WANTED

RADIOCHEMIST/RESEARCHER. PhD in Radiochemistry; four years radiochemical research experience which includes protein purification, antibody fragmentation, immunoassay (RIA and ELISA), and high level radioisotope production and purification; and proficiency in protein purification and radiolabeling with radionuclides, working with high levels of radioactivity, and with chromatographic techniques and spectroscopic methods, including HPLC, UV, IR, NMR and MS. Los Angeles, California. $48,000 per year. Send résumé to Number 65, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN FRANCISCO AREA. Family Practitioner or Primary Care Internist to join established, progressive six-physician group practice in lovely coastside community of Half Moon Bay, 25 miles south of San Francisco. CV to Larry Casalino, MD, 225 S. Cabrillo Hwy, 100A, Half Moon Bay, CA 94019.

BC/BE INTERNIST with an interest in noninvasive Cardiology currently being sought for a large metropolitan area in the southwest. The opportunity is available for a full affiliation with this state-of-the-art group of physicians with a fully-established practice. Please forward current CV to Number 66, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE INTERNIST/PRIMARY CARE PROVIDER. A three-physician group is seeking a fourth physician to join a well-established practice. Practice is located in Albuquerque, New Mexico. Wide range of recreational and cultural activities. For further information, please respond to Number 67, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEUROLOGIST. Visalia Medical Clinic, Inc, a 37-physician multispecialty group, is searching for a Neurologist to enter an active practice. Located in the San Joaquin Valley in California and serving a market area of approximately 350,000. Excellent hospital services and facilities. BC/BE. Compensation is incentive oriented with rapid advancement to full partnership. Excellent fringe benefits. Please respond to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

FRESNO COUNTY DEPARTMENT OF HEALTH is seeking a Family Practice physician for a contract position in rural health center. Be part of a teaching team in busy clinic setting adjacent to district hospital. 20 minutes from metro Fresno. Must be BC, residency trained. Contract range $60,000—$70,000 to start. Benefits include five weeks unscheduled time (vacation, sick leave, CME); 10 paid holidays; malpractice liability covered by County. Send CV and copy of California license to Donn Cobb, MD, MPH, Health Officer, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

CALIFORINA. FULL-TIME EM ATTENDING POSITION available at 233-bed teaching hospital in the heart of the San Joaquin-Sacramento River Delta. $75,000-$100,000 plus per year with flexible scheduling, camaraderie and paid malpractice. Send CV to Richard Buys, MD, PO Box 1020, Stockton, CA 95201 or call (209) 468-6818. Affirmative Action/Equal Opportunity Employer.

SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in Southern California. CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Suite 400-49
Glendale, CA 91203

PHYSICIANS WANTED

URGENT CARE CENTER. Phoenix, Arizona area. Career opportunity for the right physician with Family Practice background. Please send CV in confidence to Executive Director, Urgent Care, Mercy Services Corporation—Phoenix, 555 W. Catalina Dr, Ste 204, Phoeniz, AZ 85013.

INTERNIST. We are seeking a BC or BE General Internist to join our hospital and clinic-based group of 13 in providing primary patient care with active participation in a university affiliated teaching program. We invite all applicants but desire an enthusiastic clinician role model with excellent communication skills interested in patient care and teaching. Competitive salary and excellent fringe benefits. Send CV to Kent Imai, MD, Department of Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose, CA 95128.

ENDOCRINOLOGIST. Full-time BC/BE Endocrinologist for specialty practice in the metropolitan Phoenix area. Emphasis on all areas of Clinical Endocrinology, diabetes, and research. Laboratory and diabetes education program. Salary negotiable. Position available immediately. Send CV to Number 63, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEPHROLOGIST. Full-time BC/BE Endocrinologist for specialty practice in the metropolitan Phoenix area. Large acute and chronic dialysis. CAPD, and transplantation patient load. Salary negotiable. Send CV to Number 64, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN DIEGO, CALIFORNIA. Career opportunities for full-time Family Practitioners and Internists to work in satellite ambulatory care centers with prestigious San Diego hospital. Send CV in confidence to Mercy CarePoint Medical Group, 681 Encinitas Blvd, Ste 406-N, Encinitas, CA 92024.

HOUSE CALLS AMERICA. Want to avoid the expense and confinement of owning an office, but still wish to be your own employer? Make house calls! Become a member of a house call network that operates throughout California. Your time is your own. Set your own fees. We supply the patients and advertising. You benefit by being associated with our recognizable name. For more information write to House Calls America, Attn: Vice President of Personnel, PO Box 2401, San Bernardino, CA 92406.

NEVADA—EMERGENCY MEDICINE. An Emergency Department full-time staff position and medical directorship opportunities are currently available at client hospital in Fallon, Nevada, located one hour east of Reno. Full-service community hospital with low-volume Emergency Department. Competitive rate of reimbursement, occurrence malpractice insurance coverage, CME allowance. Director also receives health benefits, which include dependents. For more details, contact George Tracy, Spectrum Emergency Care, 6275 Lehman Dr, Ste C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

BC/BE GENERAL INTERNIST with or without subspecialty, to associate with five-man Internal Medicine group in small northern California city. Modern, complete and expanding hospital. Generous salary plus percentage. Early partnership. Please reply to Number 62, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WYOMING—EMERGENCY MEDICINE. A full-time emergency department opportunity currently exists at client hospital in Rock Springs, Wyoming. Full-service community hospital with a moderate volume emergency department. Guaranteed rate of reimbursement, occurrence malpractice insurance coverage, CME allowance. For more details, contact Mary Lou Doehrman, Spectrum Emergency Care, 6275 Lehman Dr, Ste C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

PHYSICIANS WANTED

INTERNIST—PED/OB DESIRED

Busy practice waiting for associate to share large patient load and cross coverage. Colusa is a rural area with a population base of 15,000, conveniently located near San Francisco, Lake Tahoe and Sacramento, on the scenic Sacramento River. Located on the Pacific Flyway, Colusa is known for its hunting, fishing, boating and wilderness activities. The life-style is family oriented with quality schools, services and parks in abundance.

Colusa Community Hospital is a modern, viable 56-bed facility with excellent specialty coverage, OB and ICU services. Financial incentives include: salary guarantees, start-up expenses, and assistance. Immediate opening. Contact

Donald H. Marks, MD, PhD
124 E. Webster St, Colusa, CA 95932
(916) 458-2169

APPLICATIONS ARE SOLICITED for the position of Chief of Staff at the Martinez VA Medical Center and Associate Dean for VA Affairs at the UC Davis School of Medicine. This position is jointly recruited with UC Davis, and will carry an academic appointment appropriate to the individual's qualifications. The candidate must be BC and have experience or demonstrate potential in the coordination and administration of academic and patient care programs with broad executive authority to direct utilization of resources to achieve institutional goals. The level of appointment will be commensurate with prior educational, clinical and administrative experience. Please send CV to Edward C. Gomez, MD, PhD, Associate Dean, Clinical Education, UCD, c/o VA Medical Center (11), 150 Muir Rd, Martinez, CA 94553. The VA is an Affirmative Action/Equal Opportunity Employer. Applications will not be accepted after December 30, 1987.

CALIFORNIA. Emergency Medicine Faculty Positions. Immediate opportunities available for career-oriented Emergency Physicians who possess excellent clinical and teaching skills to join the faculty of Emergency Medicine department. BC in Family Practice, Internal Medicine, Surgery, and/or BE in Emergency Medicine. Our facility, located in southern California, averages 38,000 Emergency Department visits per year, is a level II trauma center, regional burn center and Neonatology Intensive Care center. These positions require a teaching commitment in a university-affiliated Family Practice training program. We offer a competitive remuneration package to include salary, malpractice insurance, time off and flexible scheduling. Send CV to Empire Medical Group, PO Box 3571, San Bernardino, CA 92413.

Ads Get Results!

CLASSIFIED INFORMATION
(415) 863-5522 EXTENSION 244

(Continued on Page 508)

Significant reduction in angina attacks...

- All-day, all-night protection
- Few CNS side effects*
- Once-a-day convenience

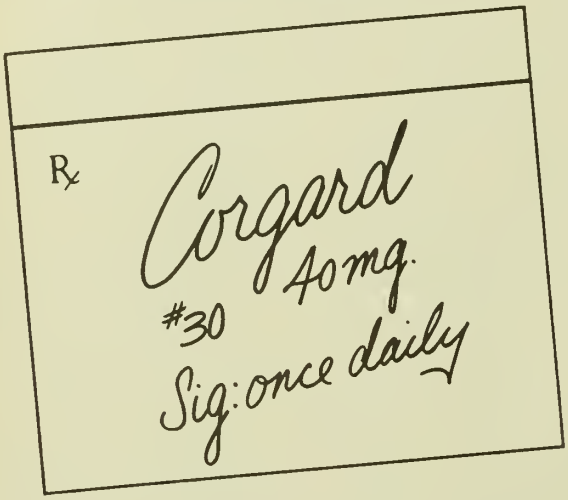
*The most commonly reported side effects, dizziness and fatigue, have been reported in approximately 2 of 100 patients receiving **CORGARD**.

CORGARD®
(nadolol tablets)
Advantages beyond control

For a complete discussion of **CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS,** and **WARNINGS,** including avoidance of abrupt withdrawal, please see brief summary on adjacent page.

NOW MEDI-CAL APPROVED

CORGARD®
(nadolol tablets)
Advantages beyond control for the angina patient



CORGARD® TABLETS
Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect, monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.
(J4-156)

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(Continued from Page 504)

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(Continued on Page 509)

(Continued from Page 508)

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 9-11, 1988, Loew's Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1988, date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1988, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1987, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1988, Laughlin.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1988, Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1988, date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1988, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1988, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

AMA ADVISORS 407

AUDIO DIGEST 393

CIBA PHARMACEUTICAL COMPANY
Transderm-Nitro 417, 418

CLASSIFIED ADVERTISING 500, 502, 504, 508, 509

CNA INSURANCE 411

COOPERATIVE OF AMERICAN PHYSICIANS 391

DISABILITY INSURANCE SERVICES, INC. 491

THE DOCTORS' COMPANY 419

ELI LILLY & COMPANY
Ceclor 499

FAMILY PRACTICE RECERTIFICATION 493

FHP PROFESSIONALS 415

GEIGY PHARMACEUTICALS
Lopressor 405, 406

GENERAL MED 418

GLAXO
Trandate 496, 497, 498
Zantac 401, 402, 403, 404

HOFFMANN-LA ROCHE LABORATORIES
Rocephin . . . . . 3rd and 4th covers

MERCK, SHARP AND DOHME
Vasotec 387, 388, 389, 390

POSTGRADUATE MEDICINE 503

JM PRINCETON COMPANY 386

PRINCETON PHARMACEUTICALS
Corgard 505, 506

A. H. ROBINS COMPANY
Micro-K 394

SCHERING LABORATORIES
Normodyne 412, 413, 414

SMITHKLINE BECKMAN
Dyazide 422

SOUTHERN CALIFORNIA PHYSICIANS
INSURANCE EXCHANGE 489

E. R. SQUIBB & SONS
Capoten 396, 397, 398

UNITED STATES AIR FORCE 507

UNITED STATES AIR FORCE RESERVE 418

UNITED STATES ARMY 501

UPJOHN COMPANY
Micronase 421
Motrin 408, 409, 410
Xanax . . . . . 2nd cover, 385, 386

THE WESTERN JOURNAL OF MEDICINE 495

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MICROBIOLOGY The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis Ceftriaxone has a high degree of stability in the presence of beta lactamases both penicillinases and cephalosporinases, of gram negative and gram positive bacteria Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage)

GRAM NEGATIVE AEROBES Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*

Note Many strains of the above organisms that are multiply resistant to other antibiotics, e g penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

GRAM POSITIVE AEROBES Staphylococcus aureus (including penicillinase-producing strains) and *Staphylococcus epidermidis* (Note methicillin resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

GRAM NEGATIVE AEROBES Citrobacter freundii, Citrobacter diversus, Providencia species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*) *Shigella* species and *Acinetobacter calcoaceticus*

ANAEROBES Bacteroides species, *Clostridium* species (Note most strains of C *difficile* are resistant)

SUSCEPTIBILITY TESTING Standard susceptibility disk method Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility One such procedure (Bauer AW Kirby WMM Sherris JC, Turck M Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45 493 496. 1966, Standardized Disk Susceptibility Test, *Federal Register* 39 19182 19184 1974 National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria

1 Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy
2 Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine) in which high antibiotic levels are attained
3 Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftriaxone disk since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone

Standardized procedures require use of control organisms The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922 *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively

DILUTION TECHNIQUES Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g, urine) in which high antibiotic levels are attained

E coli ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests Greater than 95% of MICs for the *E coli* strain should fall within the range of 0 016 to 0 5 mcg/ml The range for the *S aureus* strain should be 1 to 2 mcg/ml while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml

INDICATIONS AND USAGE Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

PROPHYLAXIS The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

ROCEPHIN® (ceftriaxone sodium/Roche)

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe oral vancomycin is the treatment of choice for antibiotic associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction however in patients with both hepatic dysfunction and significant renal disease Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are however no adequate and well controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates infants and children have been established for the dosages described in the Dosage and Administration section

ADVERSE REACTIONS Rocephin is generally well tolerated In clinical trials, the following adverse reactions which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS —pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after IV administration

HYPERSENSITIVITY —rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC —eosinophilia (6%) thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia lymphopenia thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL —diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC —elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL —elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM —headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY —moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS —diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time jaundice glycosuria hematuria, bronchospasm, serum sickness abdominal pain, colitis, flatulence dyspepsia palpitations and epistaxis

DOSAGE AND ADMINISTRATION Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams) given in divided doses every 12 hours

Generally Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g, dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1962 01)
Vials containing 500 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1963 01)
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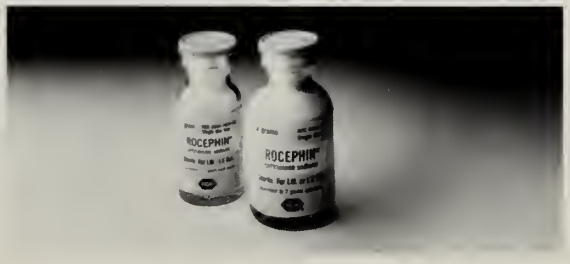

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Please see adjacent page for summary of product information.

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SEE PAGE 548

DISPLAY SHELVES

The Western Journal of Medicine

VOLUME 147 • NUMBER 5 NOVEMBER 1987

CLINICAL INVESTIGATION

549 Low Blood Mononuclear Cell Magnesium Content and Hypocalcemia in Normomagnesemic Patients
E RYZEN, T A NELSON and R K RUDE

CLINICAL MEDICINE

554 Plague Meningitis—A Retrospective Analysis of Cases Reported in the United States, 1970-1979
T M BECKER, J D POLAND, T J OUAN, M E WHITE, J M MANN and A M BARNES

558 Group B Streptococcal Soft Tissue Infections Beyond the Neonatal Period
J B McCARTY and J HABER

MEDICAL PROGRESS

561 Treatment of the Obstructive Sleep Apnea Syndrome
R V WIGGINS and W W SCHMIDT-NOWARA

CLINICAL REVIEW

569 Clinical Disorders of Phosphorus Metabolism
G C YU and D B N LEE

577 Editorial Comment: 'Moderate' Hypophosphatemia—Not Always an Innocent Bystander
R C MORRIS, Jr

MEDICAL STAFF CONFERENCE

580 Advances in the Prenatal Diagnosis of Sickle Cell Anemia
Discussant: S H EMBURY

EPITOMES

584 Important Advances in Radiology

EDITORIALS

588 A Profession Responding to Stress • The Treatment of Obstructive Sleep Apnea—Who, When, How? • Of Epidemics and Politicians

CASE REPORTS

591 Traumatic Hypopituitarism Due to a Gunshot Wound
D TRUJILLO-JUAREZ, F L CULLER, R S GANELIN and K L JONES

593 Hypernatremia Associated With Cathartics in Overdose Management
J W CALDWELL, A J NAVA and D D DE HAAS

596 Rhabdomyosarcoma of the Heart With Cerebral Metastases
S J GEYER

CORRESPONDENCE

598 Carpal Tunnel Syndrome • Criteria for Brain Death • Soviet Medicine • Use and Safety of Miconazole During Pregnancy • Condom Use, Not Barrier Method, To Prevent Heterosexual HIV Infection • 'Screening' and 'Routine' Testing • Phosphorus and Water • More Insects in the Operating Room

HEALTH CARE DELIVERY

602 Categorization of Hospital Emergency Services—Developing Valid Criteria
R M RINER, K M COLLINS, G E FOULKE, G V MOORHEAD and P TERRY

MEDICAL EDUCATION

609 Sufficiency of Clinical Literature on the Appropriate Uses of Six Medical and Surgical Procedures
A FINK, R H BROOK, J KOSECOFF, M R CHASSIN and D H SOLOMON

PUBLIC HEALTH

615 Chemical Contamination of California Drinking Water
H H RUSSELL, R J JACKSON, D P SPATH and S A BOOK

ORIGINAL ESSAY

623 First Case
H SCHNEIDERMAN

OTHER FEATURES

542 In Memoriam

634 Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming

642 Classified Advertising

652 Western State Medical Associations' Meetings

Book Reviews: 568, 622, 624

Detailed Table of Contents: 519, 522, 533

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References: 1. Zimmermon AM: *Curr Ther Res 13*: 18-22, Jon 1971 2. Amrein R, *et al. Drugs Exp Clin Res 9* (1): 85-99, 1983 3. Greenblott DJ, Allen MD, Shoder RI: *Clin Pharmacol Ther 21*: 355-361, Mor 1977.

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Warnings: Coution potients obout possible combined effects with olcohol ond other CNS depressonts. An odditive effect moy occur if olcohol is consumed the doy following use for nighttime sedotion. This potentiol moy exist for severol doys following discontinuotion. Caution ogoinst hozordous occupotions requiring complete mentol olertness (*e.g.*, operoting mochinery, driving). Potentiol impoirment of perfomonce of such octivities moy occur the doy following ingestion. Not recommended for use in persons under 15 yeors of oge. Withdrowol symptoms rorely reported; obrupt discontinuation should be ovoided with groduol topering of dosoge for those potients on medicotion for o prolonged period of time. Use coution in odministering to oddiction-prone individuols or those who might increose dosoge.

Precautions: In elderly ond debilitoted potients, it is recommended thot the dosoge be limited to 15 mg to reduce risk of oversedotion, dizziness, confusion ond/or otoxio. Consider potentiol odditive effects with other hypnotics or CNS depressonts. Employ usuol precoutions in severely depressed patients, or in those with lotent depression or suicidol tendencies, or in those with impoired renol or hepotic function.

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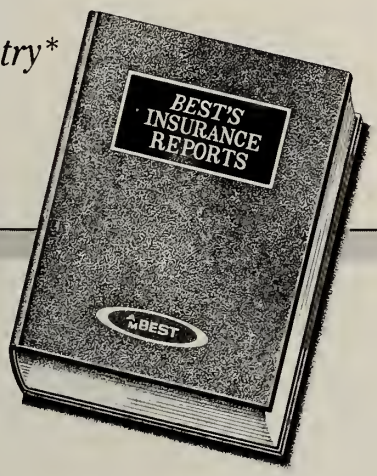

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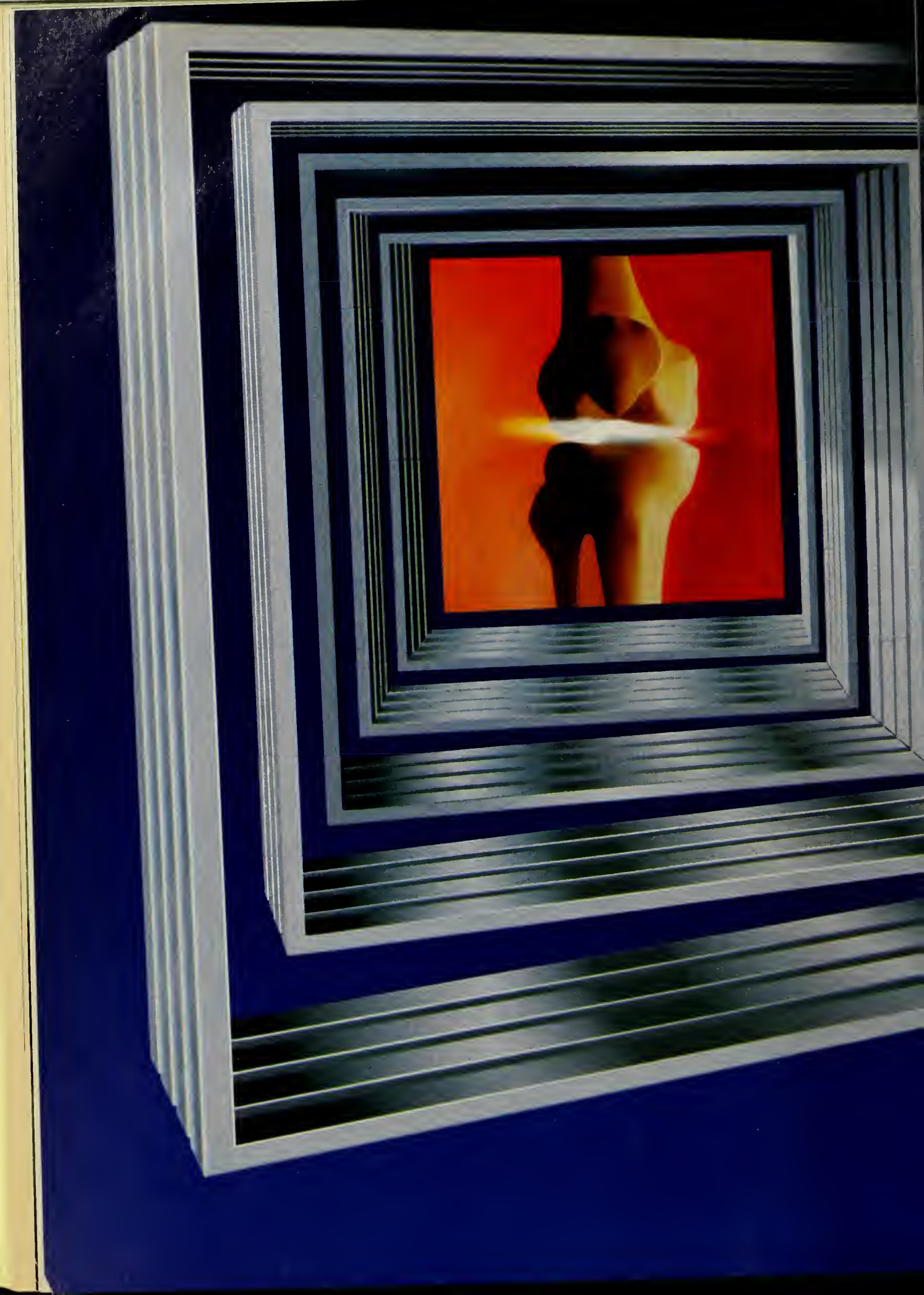

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(ibuprofen)

CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MOTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship

GASTROINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1% Probable Causal Relationship**

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1% – Causal Relationship Unknown*

GASTROINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

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CONTENTS

CLINICAL INVESTIGATION

549 **Low Blood Mononuclear Cell Magnesium Content and Hypocalcemia in Normomagnesemic Patients**
ELISABETH RYZEN, MD; TONY A. NELSON, MD, and ROBERT K. RUDE, MD
From the Departments of Medicine and Health Services, Los Angeles County-University of Southern California Medical Center, and the Orthopaedic Hospital/Bone and Connective Tissue Research Laboratories, Los Angeles.

CLINICAL MEDICINE

554 **Plague Meningitis—A Retrospective Analysis of Cases Reported in the United States, 1970-1979**
THOMAS M. BECKER, MD, PhD; JACK D. POLAND, MD, MPH; THOMAS J. QUAN, PhD; MARK E. WHITE, MD; JONATHAN M. MANN, MD, MPH, and ALLAN M. BARNES, PhD
From the Plague Branch, Division of Vector-Borne Viral Diseases, Center for Infectious Diseases, Public Health Service, US Department of Health and Human Services, Fort Collins, Colorado; the Department of Internal Medicine, Booth Memorial Hospital, Flushing, New York, and the Center for Prevention Services, Division of Sexually Transmitted Diseases, and the Center for Infectious Diseases, Centers for Disease Control, Atlanta.

558 **Group B Streptococcal Soft Tissue Infections Beyond the Neonatal Period**
JAMES B. McCARTY, MD, and JUDY HABER, PhD
From the Departments of Pediatrics and Microbiology, Valley Medical Center, University of California, San Francisco/Fresno-Central San Joaquin Valley Medical Education Program, Fresno, California.

MEDICAL PROGRESS

561 **Treatment of the Obstructive Sleep Apnea Syndrome**
ROBERT V. WIGGINS, MD, and WOLFGANG W. SCHMIDT-NOWARA, MD
From the Division of Otolaryngology, Departments of Surgery and Medicine, Center for Otolaryngology and Communicative Disorders, University of New Mexico School of Medicine, Albuquerque.

CLINICAL REVIEW

569 **Clinical Disorders of Phosphorus Metabolism**
GEORGE C. YU, MD, and DAVID B. N. LEE, MD
From the Department of Medicine, Pulmonary Division, Wadsworth Veterans Administration Medical Center, and the Department of Medicine, Division of Nephrology, UCLA-San Fernando Valley Medical Program, University of California, Los Angeles, School of Medicine.

577 **Editorial Comment: 'Moderate' Hypophosphatemia—Not Always an Innocent Bystander**
R. CURTIS MORRIS, Jr, MD
From the General Clinical Research Center, Departments of Medicine and Pediatrics and the Cancer Research Institute, University of California, San Francisco, School of Medicine.

MEDICAL STAFF CONFERENCE

580 **Advances in the Prenatal Diagnosis of Sickle Cell Anemia**
Discussant: STEPHEN H. EMBURY, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine.

(Continued on Page 522)

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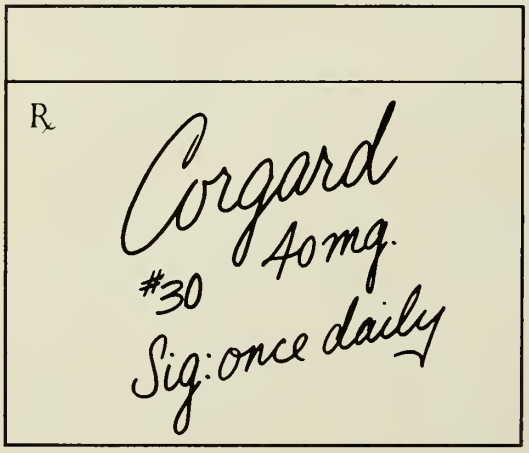

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WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets. (J4-156)

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CONTENTS

(Continued from Page 519)

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Radiology

Items of progress in radiology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

584 **Angiographic Diagnosis and Therapy for Impotence**
JOSEPH J. BOOKSTEIN, MD, and ALAN LURIE, MD

584 **Duplex Sonographic Diagnosis of Deep Venous Thrombosis of the Leg**
R. BROOKE JEFFREY, Jr, MD

585 **Magnetic Resonance Imaging and Pelvic Abnormalities**
HEDVIG HRICAK, MD

585 **Magnetic Resonance of the Liver**
ALBERT A. MOSS, MD

586 **Temporomandibular Joint Radiology Update**
JOSEPH R. THOMPSON, MD

586 **Prenatal Diagnosis of Central Nervous System Abnormalities**
RONALD R. TOWNSEND, MD, and ROY A. FILLY, MD

586 **Percutaneous Gastrostomy**
HAROLD COONS, MD

587 **New Developments in Contrast Media**
SACHIKO T. COCHRAN, MD

EDITORIALS

588 **A Profession Responding to Stress**

588 **The Treatment of Obstructive Sleep Apnea—Who, When, How?**
ELIOT A. PHILLIPSON, MD
From the Department of Medicine, University of Toronto, Toronto, Ontario.

590 **Of Epidemics and Politicians**

CASE REPORTS

591 **Traumatic Hypopituitarism Due to a Gunshot Wound**
DANIEL TRUJILLO-JUAREZ, MD; FLOYD L. CULLER, MD; ROBERT S. GANELIN, MD, and KENNETH L. JONES, MD
From the Division of Pediatric Endocrinology, Department of Pediatrics, University of California, San Diego, School of Medicine; the Whittier Institute for Diabetes and Endocrinology, La Jolla, California, and the Hamad General Hospital, Doha, Qatar.

593 **Hypernatremia Associated With Cathartics in Overdose Management**
JOHN W. CALDWELL, PharmD; ADOLPH J. NAVA, MD, and DAVID D. DE HAAS, MD
From the Department of Medicine, Kern Medical Center, Bakersfield, California, and the University of California, Los Angeles, School of Medicine.

596 **Rhabdomyosarcoma of the Heart With Cerebral Metastases**
STANLEY J. GEYER, MD
From the Laboratory Service, Veterans Administration Medical Center, and the Department of Pathology, University of Washington School of Medicine, Seattle.

CORRESPONDENCE

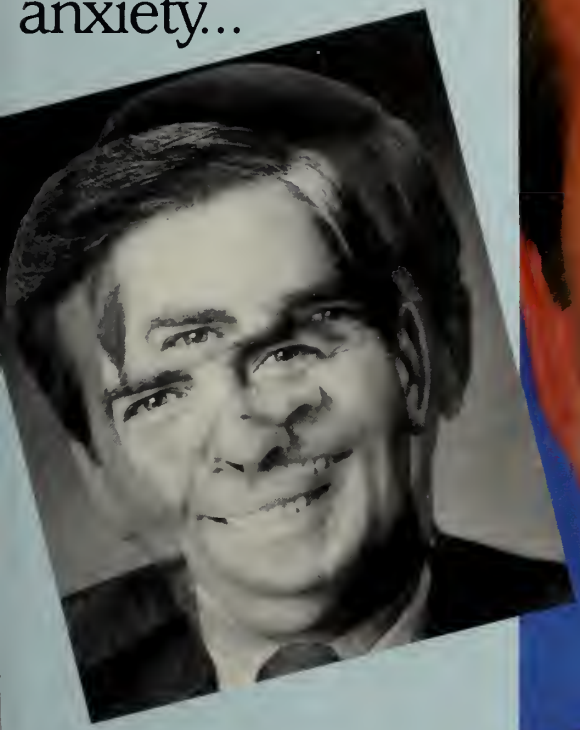
598 **Carpal Tunnel Syndrome**
PETER A. NATHAN, MD

598 **Criteria for Brain Death**
LAWRENCE F. MARSHALL, MD

598 **Soviet Medicine**
ALAN P. ZELICOFF, MD

(Continued on Page 533)

In the treatment of chronic anxiety...



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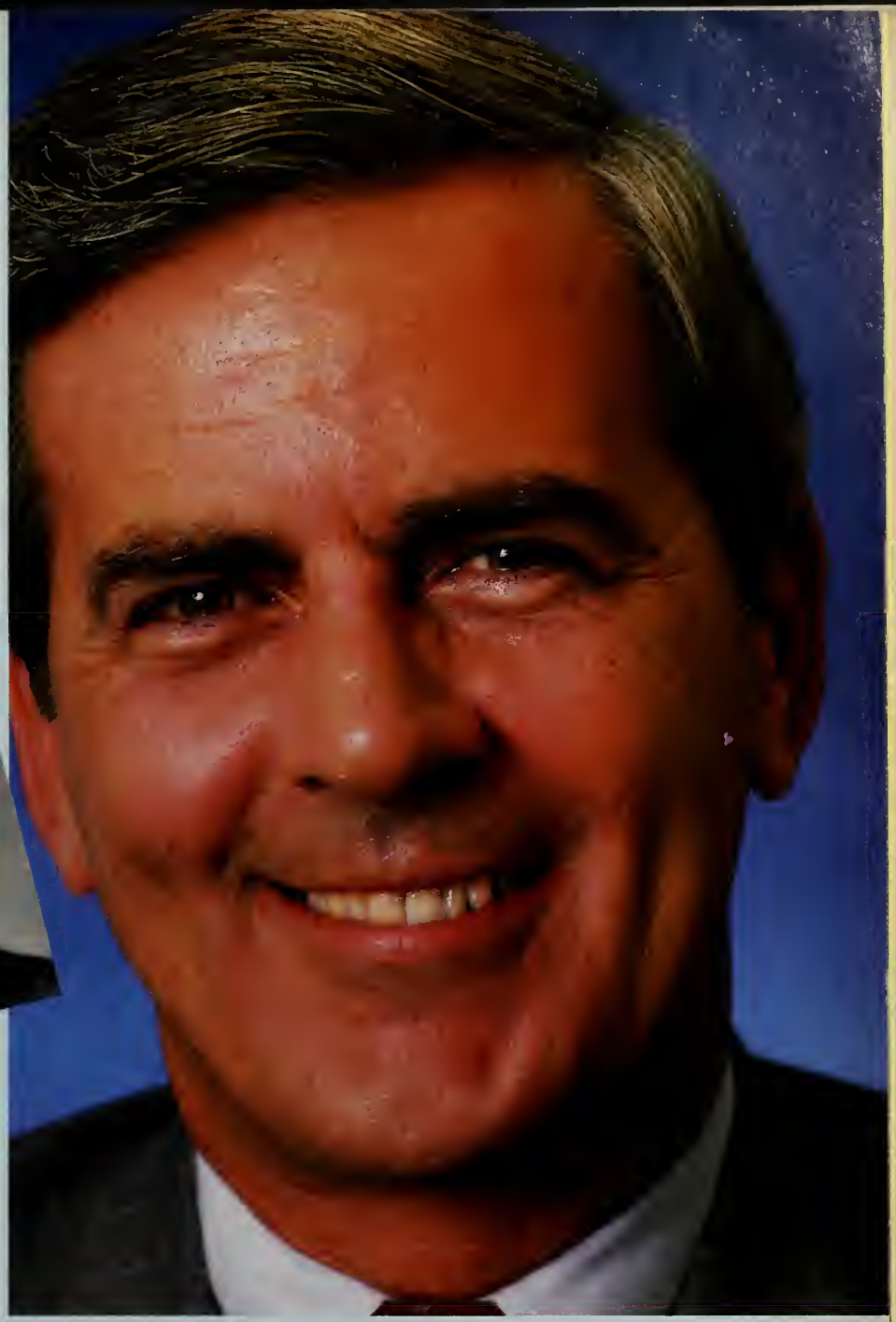

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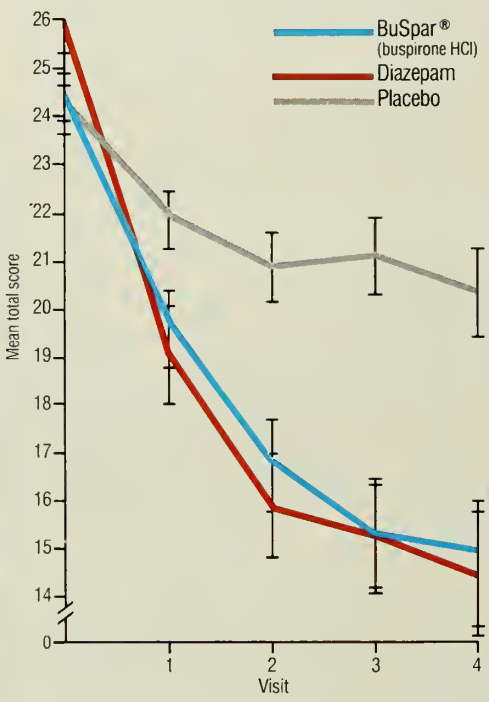
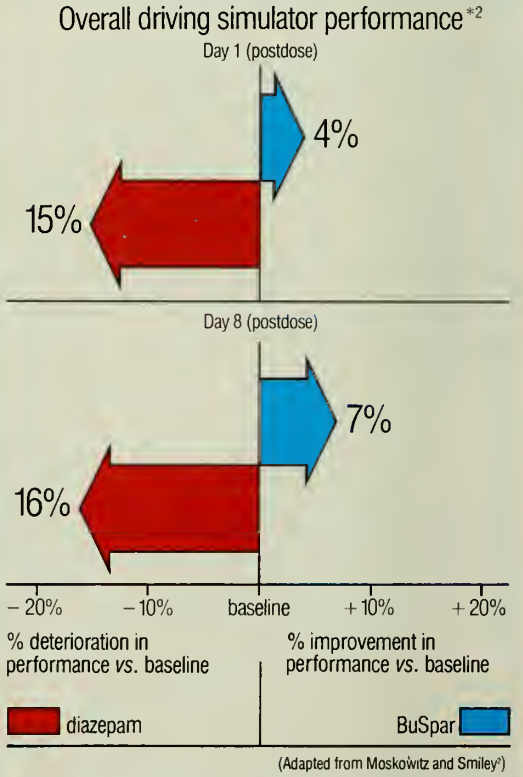


Hamilton Anxiety Scale—total scores



(Adapted from Moskowitz and Smiley[2])

*Study conducted in normal volunteers: Three of the 20 simulator variables (total lane exceedances, total time out of lane, coherence) were excluded from composite analysis due to significant pretreatment differences.

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References: 1. Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12,Sec 2):81-86. **2.** Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12,Sec 2):45-55. **3.** Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. **4.** Cole JO, et al: Assessment of the abuse liability of buspirone in recreational sedative users. *J Clin Psychiatry* 1982;(12,Sec 2):69-74. **5.** Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **6.** Mattila MJ, et al: Acute effects of buspirone and alcohol on psychomotor skills. *J Clin Psychiatry* 1982;(12,Sec 2):56-60. **7.** Data on file, Mead Johnson Pharmaceuticals.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients. Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, light-headedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, light-headed feeling, gastrointestinal disturbances (1.2%), primarily nausea, miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows. Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGDT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

Mead Johnson PHARMACEUTICALS
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Many groups TALK about building a better America—The Army Reserve WORKS at it.

24-hour security for the hypertensive heart

First-step cardiovascular protection

Reduces workload of the heart by reducing myocardial O_2 demand

Preserves K^+ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please consult Brief Summary of Prescribing Information on the following page.

Once-a-day in hypertension...

Lopressor®
metoprolol tartrate

Changing the Course of Cardiovascular Care

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First-step protection for the hypertensive heart

Lopressor®
metoprolol tartrate USP

Tablets
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.
Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.
During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.
Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.
If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.
Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.
No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)
Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.
Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.
Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.
There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.
The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.
Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.
Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.
Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.
Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.
Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.
Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.
In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).
On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:
Elimination of the Drug: Gastric lavage should be performed.
Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.
Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.
Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Geigy
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
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CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Only one tablet at bedtime

Controls nocturnal acid to relieve pain and heal duodenal ulcers

Heals active duodenal ulcers after 4 weeks in most patients*[1]

ZANTAC 300 mg h.s.	*270/320*	*84%*
ZANTAC 150 mg b.i.d.	*292/345*	*85%*

In well-controlled, double-blind, multicenter trials, ZANTAC 300 mg h.s. healed active duodenal ulcers in 84% of patients after 4 weeks. After 8 weeks, healing rates may be higher with ZANTAC 150 mg b.i.d. (92%) than with ZANTAC 300 mg h.s. (87%).

Relieves pain and other symptoms as effectively as ZANTAC 150 mg b.i.d.[1]

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Once-daily dosing may enhance compliance in patients for whom dosing convenience is important

Side-effects profile comparable to ZANTAC 150 mg b.i.d.[1-3]

Headache—sometimes severe—has been reported. Rare effects on the CNS, cardiovascular, GI, hepatic, and integumental systems have been observed, as well as rare cases of hypersensitivity reactions. See ADVERSE REACTIONS section of Brief Summary of Product Information before prescribing.

No significant interference with the hepatic cytochrome P-450 enzyme system at recommended doses

ZANTAC 300 mg h.s. had no significant drug interactions with theophylline or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications which decrease gastric acidity are administered.

not known exactly how much acid inhibition eded to heal ulcers.

Glaxo / ROCHE

See next page for references and Brief Summary of Product Information.

IN ACTIVE DUODENAL ULCERS

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets

References: 1. Data available on request, Glaxo Inc. **2.** Ireland A, Colin-Jones DG, Gear P, et al: Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984;2:274-275. **3.** Colin-Jones DG, Ireland A, Gear P, et al: Reducing overnight secretion of acid to heal duodenal ulcers. *Am J Med* 1984;77 (suppl 5B):116-122.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC® (ranitidine hydrochloride) and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

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Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

August 1987

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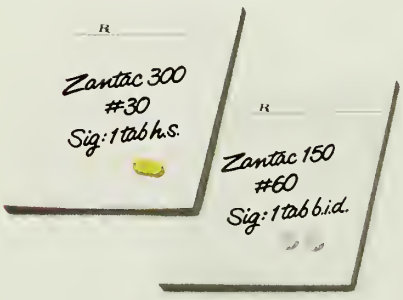

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The Western Journal of Medicine

CONTENTS

(Continued from Page 522)

599 **Use and Safety of Miconazole During Pregnancy**
RONALD E. AINSWORTH, MD
PETER J. JEWESSON, PhD(Pharm), and ANTHONY W. CHOW, MD, FRCP(C), Reply

600 **Condom Use, Not Barrier Method, To Prevent Heterosexual HIV Infection**
JEFFREY S. GREENSPOON, MD, and GERALD S. BERNSTEIN, MD

600 **'Screening' and 'Routine' Testing**
R. E. HOROWITZ, MD
H. BRAUNSTEIN, MD

601 **Phosphorus and Water**
CAROLYN CSONGRADI

601 **More Insects in the Operating Room**
JOHN BLOSSOM, MD

HEALTH CARE DELIVERY

602 **Categorization of Hospital Emergency Services—Developing Valid Criteria**
R. MYLES RINER, MD; KATHRYN MAINO COLLINS, RN; GARRETT E. FOULKE, MD; GEORGE V. MOORHEAD, MPH, and PHILLIP TERRY, MA
From the California Emergency Physicians Medical Group and the Emergency Department, Doctor's Medical Center, Modesto; the Emergency Department, St Joseph's Medical Center, Stockton; the Section of Critical Care, Division of Emergency Medicine/Clinical Toxicology, Department of Internal Medicine, University of California, Davis Medical Center, and the California Emergency Medical Services Authority, Sacramento, California.

MEDICAL EDUCATION

609 **Sufficiency of Clinical Literature on the Appropriate Uses of Six Medical and Surgical Procedures**
ARLENE FINK, PhD; ROBERT H. BROOK, MD, ScD; JACQUELINE KOSECOFF, PhD; MARK R. CHASSIN, MD, MPH, and DAVID H. SOLOMON, MD
From the Departments of Economics and System Sciences, The Rand Corporation, Santa Monica, California, and the Departments of Medicine and Public Health, Center for the Health Sciences, University of California, Los Angeles.

PUBLIC HEALTH

615 **Chemical Contamination of California Drinking Water**
HANAFI H. RUSSELL; RICHARD J. JACKSON, MD, MPH; DAVID P. SPATH, PhD, and STEVEN A. BOOK, PhD
From the Community Toxicology Unit, Hazard Evaluation Section, Sanitary Engineering Branch, and the Office of Environmental Health Hazard Assessment, Department of Health Services, Berkeley, California.

ORIGINAL ESSAY

623 **First Case**
HENRY SCHNEIDERMAN, MD
From the Departments of Medicine and Pathology, University of Connecticut Health Center, Farmington, Connecticut.

OTHER FEATURES

542 **In Memoriam**

634 **Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming**

642 **Classified Advertising**

652 **Western State Medical Associations' Meetings**

Book Reviews: 568, 622, 624

★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

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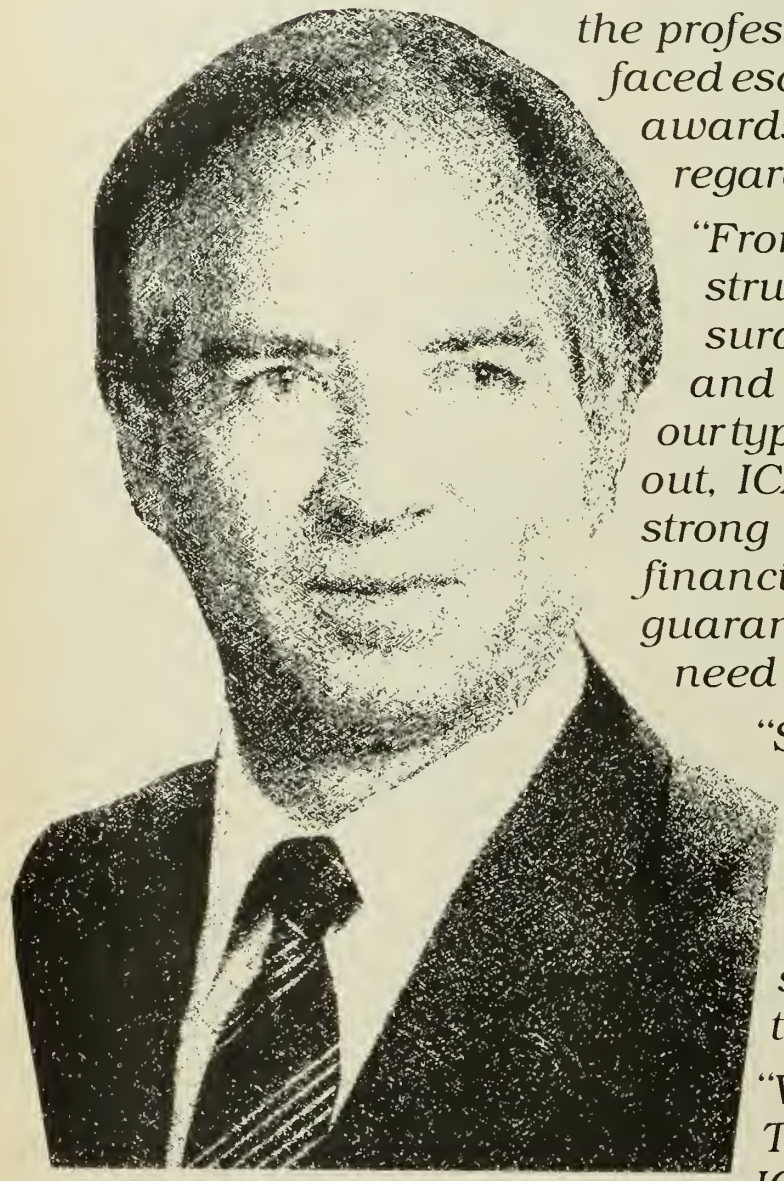

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VASOTEC is contraindicated in patients who are hypersensitive to this product.

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme (ACE) inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC in clinical trials). In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. In using VASOTEC, consideration should be given to the fact that another ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and the available data are insufficient to show that VASOTEC does not have a similar risk (see WARNINGS).

Discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product.

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Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose. (See WARNINGS and DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC® (Enalapril Maleate, MSD) has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials or since the drug was marketed include:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Renal: Renal dysfunction, renal failure, oliguria. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Other: Dyspnea, muscle cramps, hyperhidrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Dosage and Administration: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg (break the 5-mg tablet) should be used under medical supervision for at least one hour to determine whether excess hypotension will occur. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily. For dialysis patients, the initial dose and the dose on dialysis days is 2.5 mg/day. Dosage on nondialysis days should be adjusted depending on blood pressure response.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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An Anaprox kind of pain

Fast-acting non-narcotic* pain relief as effective as the codeine combinations.

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Usually all you need for mild-to-moderate pain

275 MG TABLETS

Anaprox®

(NAPROXEN SODIUM)

DOSAGE/STAT 2 tab/THEN q 6-8h

*ANAPROX® (naproxen sodium) is a nonsteroidal anti-inflammatory agent that has been developed as an analgesic and possesses antipyretic properties.

For brief summary of prescribing information, please see next page.

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Brief Summary: ANAPROX® (naproxen sodium)
Indications: Relief of mild to moderate pain; treatment of primary dysmenorrhea.
Contraindications: Patients who have had allergic reactions to NAPROSYN or ANAPROX or in whom aspirin or other NSAIDs induce the syndrome of asthma, rhinitis, and nasal polyps.
Warnings: GI bleeding, sometimes severe, and occasionally fatal, has been reported. Do not give to patients with active peptic ulcer unless potential benefit outweighs risk. Administer to those and others with history of GI disease only under close supervision.
Precautions: DO NOT GIVE NAPROSYN® (NAPROXEN) CONCOMITANTLY WITH ANAPROX® (NAPROXEN SODIUM) SINCE BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION. Because anaphylactic reactions usually occur in patients with a history of such reactions, question patients for asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy. If such symptoms occur, discontinue the drug. Acute interstitial nephritis with hematuria, proteinuria, and nephrotic syndrome has been reported. Patients with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, discontinue the drug. Use with caution and monitor serum creatinine and/or creatinine clearance in patients with significantly impaired renal function. Use caution in patients with baseline creatinine clearance less than 20 ml/minute. Use caution when high doses are required in the elderly or in patients with chronic alcoholic liver disease or cirrhosis. With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. They may progress, remain unchanged, or be transient with continued therapy. Elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported rarely. If liver disease develops or if systemic manifestations occur (e.g., eosinophilia or rash), discontinue therapy. If steroid dosage is reduced or eliminated during therapy, do so slowly and observe patients closely for adverse effects, including adrenal insufficiency and exacerbation of arthritis symptoms. Determine hemoglobin values frequently for patients with initial values of 10 grams or less who receive long-term therapy. Peripheral edema has been reported. For patients with restricted sodium intake, note that each tablet contains approximately 25 mg (1 mEq) sodium. Use with caution in patients with fluid retention, hypertension or heart failure. The drug's antipyretic and anti-inflammatory activities may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies soon after starting therapy and at periodic intervals if the drug is used for an extended period.
Information for Patients: Patients should use caution for activities requiring alertness if they experience drowsiness, dizziness, vertigo or depression during therapy.
Drug Interactions: Use caution when giving concomitantly with coumarin-type anticoagulants; a hydantoin, sulfonamide or sulfonylurea; furosemide; lithium; beta-blockers, probenecid; or methotrexate.
Drug/Laboratory Test Interactions: The drug may decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before doing adrenal function tests. The drug may interfere with urinary assays of 5HIAA.
Carcinogenesis: A 2-year rat study showed no evidence of carcinogenicity.
Pregnancy: Category B. Do not use during pregnancy unless clearly needed. Avoid use during late pregnancy.
Nursing Mothers: Avoid use in nursing mothers.
Pediatric Use: Indications and dosage have not been established.
Adverse Reactions: Incidence Greater Than 1%: GI: The most frequent complaints related to the GI tract: constipation,* heartburn,* abdominal pain,* nausea,* dyspepsia, diarrhea, stomatitis. CNS: headache,* dizziness,* drowsiness,* light-headedness, vertigo. Dermatologic: itching (pruritus),* skin eruptions,* ecchymoses,* sweating, purpura. Special Senses: tinnitus,* hearing disturbances, visual disturbances. Cardiovascular: edema,* dyspnea,* palpitations. General: thirst. *Incidence of reported reaction 3%-9%. Where unmarked, incidence less than 3%. Incidence Less Than 1%: Probable Causal Relationship: GI: abnormal liver function tests, GI bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting. Renal: glomerular nephritis, hematuria, interstitial nephritis, nephrotic syndrome, renal disease. Hematologic: eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alopecia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever). Causal Relationship Unknown: Hematologic: agranulocytosis, aplastic anemia, hemolytic anemia. CNS: cognitive dysfunction. Dermatologic: epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, urticaria. GI: ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypoglycemia.
Overdosage: May have drowsiness, heartburn, indigestion, nausea, vomiting. Empty stomach and use usual supportive measures. Prompt administration of 5 grams activated charcoal may reduce drug absorption.
Dosage and Administration for Mild to Moderate Pain, Dysmenorrhea and Acute Tendinitis and Bursitis: The recommended starting dose is two 275 mg tablets, followed by one 275 mg tablet every 6 to 8 hours, as required. The total daily dose should not exceed 5 tablets (1375 mg).
Caution: Federal law prohibits dispensing without prescription.
See package insert for full Prescribing Information.
#24 © Revised 6/86

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SYNTEX LABORATORIES INC
PALO ALTO CA 94304

In Memoriam

California Medical Association

Bosworth, David B, Oakland. Died Jul 12, 1987, aged 75. Graduate of California College of Medicine, 1936. Dr Bosworth was a member of the Alameda-Contra Costa Medical Association.

Esslinger, Gillis A., Oakland. Died Jul 16, 1987, aged 85. Graduate of University of Kansas, Kansas City, 1928. Licensed in California in 1947. Dr Esslinger was a member of the Alameda-Contra Costa Medical Association.

Gonda, Thomas A., Stanford. Died Aug 12, 1987, aged 65. Graduate of Stanford University, 1945. Licensed in California in 1945. Dr Gonda was a member of the Santa Clara County Medical Society.

Guida, Anthony J., San Leandro. Died Jul 5, 1987, aged 62. Graduate of Creighton Medical School, Omaha, 1948. Licensed in California in 1957. Dr Guida was a member of the Alameda-Contra Costa Medical Association.

Merkley, Ralph G., Cupertino. Died Aug 6, 1987, aged 59. Graduate of Harvard Medical School, Boston, 1952. Licensed in California in 1954. Dr Merkley was a member of the Santa Clara County Medical Society.

Moose, Ray M., San Bernardino. Died Jul 14, 1987, aged 96. Graduate of University of Cincinnati, 1918. Licensed in California in 1920. Dr Moose was a member of the San Bernardino County Medical Society.

Nordstrom, Ray C., Berkeley. Died Jul 3, 1987, aged 74. Graduate of Stanford University School of Medicine, 1945. Licensed in California in 1953. Dr Nordstrom was a member of the Alameda-Contra Costa Medical Association.

Nunn, Allan T., Sacramento. Died Jul 1, 1987, aged 34. Graduate of University of California, Davis, School of Medicine, 1976. Licensed in California in 1977. Dr Nunn was a member of the Sacramento-El Dorado Medical Society.

Quirmbach, Robert P., San Jose. Died Jul 17, 1987, aged 85. Graduate of University of Colorado School of Medicine, Denver, 1931. Licensed in California in 1931. Dr Quirmbach was a member of the Santa Clara County Medical Society.

Ramirez, Xavier Hall, Bakersfield. Died Jul 10, 1987, aged 74. Graduate of Tufts Medical School, Boston, 1940. Licensed in California in 1945. Dr Ramirez was a member of the Kern County Medical Society.

Rhee, James L., Oakland. Died Jul 28, 1987, aged 69. Graduate of University of Southern California, Los Angeles, 1947. Licensed in California in 1947. Dr Rhee was a member of the Los Angeles County Medical Association.

Stengert, Krzysztof B., Davis. Died Aug 1987, aged 60. Graduate of Medical Academy, Poznan, Poland, 1962. Licensed in California in 1977. Dr Stengert was a member of the Yolo County Medical Society.

Tucker, Wilson D., San Diego. Died Aug 13, 1987, aged 74. Graduate of Hahnemann University, Philadelphia, 1941. Licensed in California in 1966. Dr Tucker was a member of the San Diego County Medical Society.

Van De Pol, Andrew, Modesto. Died Aug 10, 1987, aged 81. Graduate of University of California, San Francisco, 1933. Licensed in California in 1933. Dr Van De Pol was a member of the Stanislaus County Medical Society.

Wilson, William H., San Bernardino. Died May 9, 1987, aged 69. Graduate of University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1944. Dr Wilson was a member of the San Bernardino County Medical Society.

Wing, Willard J. Died Aug 1987, aged 54. Graduate of Tulane University School of Medicine, New Orleans, 1962. Licensed in California in 1963. Dr Wing was a member of the Orange County Medical Association.

Wise, Edith P. Died Apr 2, 1987, aged 92. Graduate of Washington University School of Medicine, St Louis, 1923. Dr Wise was a member of the Alameda-Contra Costa Medical Association.

Wolfson, Mast, Monterey. Died Apr 17, 1987, aged 94. Graduate of Harvard Medical School, 1920. Licensed in California in 1920. Dr Wolfson was a member of the Monterey County Medical Society.

Idaho Medical Association

Crowe, Frank W., Boise. Died Apr 29, 1987, aged 67. Graduate of University of Utah School of Medicine, Salt Lake City, 1949. Licensed in Idaho in 1953. Dr Crowe was a member of the Ada County Medical Society.

Espeland, Duane H., Boise. Died Apr 7, 1987, aged 54. Graduate of University of Washington School of Medicine, 1964. Licensed in Idaho in 1973. Dr Espeland was a member of the Ada County Medical Society.

Worden Donald K., Lewiston. Died Jul 21, 1987, aged 87. Graduate of University of Nebraska College of Medicine, Omaha, 1925. Licensed in Idaho in 1937. Dr Worden was a member of the North Idaho District Medical Society.

New Mexico Medical Society

Draelos, Theodore T., Silver City. Died Sep 14, 1987, aged 57. Graduate of University of Wisconsin, Madison, 1955. Dr Draelos was a member of the Grant County Medical Society.

Ydens, Jan W., Albuquerque. Died Aug 28, 1987, aged 71. Graduate of University of Leiden, Holland, 1948. Dr Ydens was a member of the Greater Albuquerque Medical Society.

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CARAFATE®
(sucralfate)

BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that the simultaneous administration of CARAFATE with tetracycline, phenytoin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. The clinical significance of these animal studies is yet to be defined.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of drug-related tumorigenicity was found in chronic oral toxicity studies of 24 months' duration conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies have not been conducted.

Pregnancy: Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients, adverse effects were reported in 121 (4.7%). Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm pink tablets are supplied in bottles of 100 and in Unit Dose Identification Paks of 100. The tablets are embossed with MARION/1712. Issued 3/84

References:
1. Grossman MI: *Scand J Gastroenterol* 58 (suppl 15):7-16, 1980.
2. Marks IN, in Hellemans J, Vantrappen G (eds): *Gastrointestinal Tract Disorders in the Elderly.* Edinburgh, Churchill Livingstone, 70-81, 1984.
3. Krentz K, Jablonowski H, in Hellemans J, Vantrappen G (eds): *Gastrointestinal Tract Disorders in the Elderly.* Edinburgh, Churchill Livingstone, 62-69, 1984.

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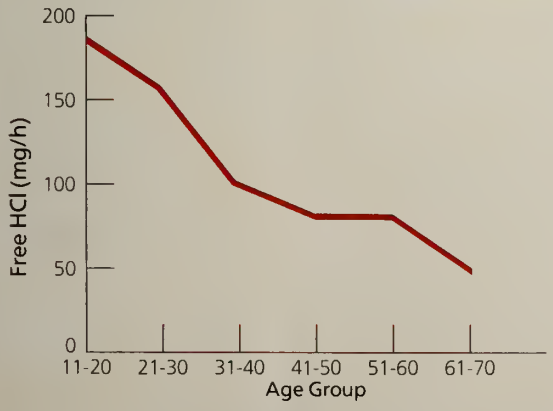
1595H7

Specialized ulcer therapy

When advancing age signals reduced acid secretion

If your duodenal ulcer patient is over 55, decreased mucosal resistance is more likely to cause an ulcer than hypersecretion of acid-pepsin.[1] A tendency toward lower acid secretion with advancing age has been shown.[2,3]

Declining gastric secretion and age[3]



CARAFATE® (sucralfate/Marion) makes sense as initial ulcer therapy for the elderly. Carafate provides ulcer healing rates comparable to H_2 antagonists without the risk of systemic side effects or drug interactions—an important benefit for older patients.

The unique, nonsystemic action of Carafate enhances the body's own ulcer healing ability, strengthening the mucosal structure as it protects damaged tissue from further injury.

When advancing age signals reduced acid secretion, choose the specialized ulcer therapy of safe, nonsystemic Carafate.

Nothing works like

CARAFATE®
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Please see adjoining page for references and brief summary of prescribing information.

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was conducted exclusively by The Upjohn Company

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Drug Formulary

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A better alternative for hypertensives who are going bananas...

Spare your patients the extra cost—in calories, sodium and dollars.

Spare your patients the rigors of dietary K^+ supplementation.

DYAZIDE®

25mg Hydrochlorothiazide/**50mg** Triamterene/SKF

Effective antihypertensive* therapy...without the bananas

* Not for initial therapy. See brief summary.

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosoria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: **'Dyazide' is supplied as a red and white capsule in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

BRS-DZ.L42

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Carolina, P.R. 00630

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

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Keeping Our Objectives in Sight

Marshall B. Block, M.D.

It was a hot Sunday in July when my folks left for my *Mother's* aunt's funeral. As they reached the top of a bridge on their way to the funeral service, the car came to a halt as the fuel tank registered empty. Luckily, the car's momentum carried it down the far side of the bridge and my father was able to get it off to the side of the road. With no gas station in sight, my father Charles sized up the situation and said, "Beatrice, we're in trouble! You stay here with the car and I'll go to the funeral!" "But Charlie, it's *my* aunt!," my mother responded.

So, too, we may be losing sight of our primary objectives with the constant barrage of changes which are affecting our professional lives. The almost daily transmittal from one health maintenance group or another regarding changes in coverage, providers, or charges is becoming a nightmare in bookkeeping. The constant "please transfer my medical record" slips crossing our desks as patients move from one plan to another as their employer seeks the cheapest rates possible is quite disheartening for those of us who try to actually "care" for our patients. Medicine has become somewhat of a revolving door as patients move from one physician to another only to return at a later date. The cost effectiveness of all these plans seems to this observer a bit in doubt as each time a patient changes physicians a new comprehensive evaluation needs to be undertaken, which is more costly than a return visit. How many times can these plans undergo such turnover and still remain viable? Worse yet, how can we as physicians maintain our professional status when we are forced to recognize that no one really cares whether *we* care. The patients' bottom line is cost. Since most are covered in large groups, there is no commitment to physician or to quality medical care. It is a frustrating situation for physicians who want to render the care that the public desires but is unwilling to acquire. The long term solution to these "wholesale" health care plans will be, I suspect, to self-destruct. We will need some more stable long term solutions to the health care dilemma that we are faced with in our country and in our locale. We are in a stopgap phase and other solutions will need to appear in order for our populace to continue to receive the quality medical care which they had obtained in the past but which is fast receding as the cost of technology and the number of physicians able to provide care has multiplied. Hopefully, after this period of unrest, uncertainty and depression, will come a better system to which we can all contribute in the manner which we have been trained. We must continue to stick to our ideals or we will lose our credibility as patient advocates. ■

Marshall B. Block, M.D., Editor

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IN THIS ISSUE

- Smart Investing
  Merrill J. Sauriol
- Risk Management
- Schizoid
  William B. McGrath, M.D.
- New Active Members
- Community Cancer Prevention
  Frank L. Meyskens, Jr., M.D.
  Louis J. Kettel, M.D.
- Physicians in the News
- Medi-Facts

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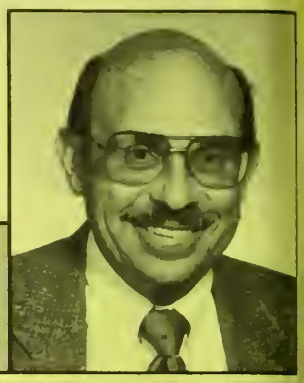

From Our President

There has been considerable turmoil among Arizona physicians concerning the increasing premiums for liability insurance charged by the Mutual Insurance Company of Arizona (MICA). Recently, much of this unrest has been fanned by a letter sent to all Arizona physicians by Howard Fischer, who represents Fairness and Accountability in Insurance Reform (FAIR), and also represents People Against Intolerable Negligence (PAIN). In his letter, Mr. Fischer attempts to show physicians that MICA is charging them unnecessarily high premiums, paying unnecessary taxes, and performing many other abuses.

In my opinion, this letter is a blatant attempt to mislead Arizona physicians and sow seeds of discontent among them towards their professional liability insurance company. I base this statement on direct, in-person contacts with MICA staff and members of the MICA Board. I have also been a guest at a meeting of the MICA Board, and can only be impressed by the hard work and integrity shown by the Board and the staff in their close and time-consuming scrutiny of all the issues they consider. Practicing physicians are strongly represented on the Board by their practicing colleagues. When premium increases are voted, those Board members must pay them like the rest of us.

It is my firm belief that Mr. Fischer's letter is not motivated by concern for Arizona physicians, but is an attempt to divert attention from a major problem, that of the proliferation of lawsuits. I see this letter as an attempt to create divisiveness among physicians in anticipation of future attempts in this state at tort reform. Although the organizations he represents purport to be lay groups, FAIR is publicly acknowledged to be financially supported by the trial lawyers. In addition, Fischer's name appears as an incorporator of PAIN in its articles of incorporation. There is certainly a large dose of trial lawyer influence in both of these groups.

Who is your ally? MICA is your ally. This company, which conducts its affairs in a business-like way, will continue to provide us insurance if allowed to remain actuarially sound, and to anticipate, as it does, the need for reserves to cover actions against physicians which are coming in at an alarming rate. Until the basic problems of using the tort system to compensate all adverse outcomes is solved, the company must remain financially capable of defending us and paying judgments when they are against us. This is the hard reality.

Who is not your ally? Howard Fischer is not your ally. PAIN is not your ally. FAIR is not your ally. Don't be seduced by their blatant attempts to mislead you. ■

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Covered-call writing was around long before standardized options in 1973 made the game easier to play. But it is attracting renewed interest because of the fat premiums bullish investors have recently been willing to pay for calls. Over the past six months, options premiums returned an average 10.24% based on the underlying stock, according to the Chicago Board Options Exchange. That is a lot better than Treasury bills, which pay about 3% in six months.

Still, covered-call writing is not as simple and carefree as parking money with Uncle Sam. Along with the possibility of watching a stock rise and be called away, you run the traditional risk that an issue will go into the tank. So if you have taken in a $4 premium on a $40 stock that drops to $35, the holder of the option certainly will not call it away, and you are a net loser of $1 per share.

Gold Lining: "In my opinion, you must like and be comfortable with the underlying stock before you think of doing a covered-call write." Stocks with long-term steady growth histories are good candidates.

But what if a stock spurts up one month after you write an option and gets called away? The silver lining: You gain the same premium for holding a contract one month instead of nine, so it works out to a higher annualized yield.

For continuing income, you will have to roll over a series of short-term contracts. And a systematic call-writing program should be large enough so profits are not eaten up by a broker's commissions.

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Risk Management

. . . or how to tip the scales of justice in your favor

"The principal shortcoming . . . is the lack of proper documentation . . . the lack of clinical record-keeping becomes acutely visible." *Newborn Neurological Deficit Study, A. Russel Locallo, J.D., M.P.H., M.S. and Joanna Siegel, B.S., S.M., Harvard Medical Institutions/Risk Management Foundation (Physician Insurers Association of America, April 1987.)*

If there is but one piece of advice risk managers would give to their physician-clients, it is this: practice good medicine and document, Document, DOCUMENT!

It is no longer enough to merely practice good medicine; physicians must record their actions to create a record of proof.

Good Records

Liability insurance officials point out that in significant cases of alleged malpractice, there is almost always one key area of information missing from the record which the physician will come to wish had been documented.

No matter what system is followed, good records all incorporate seven elements:

- **Good records are timely.** Delay exaggerates the risk of confusion or neglect of important facts, observations, or sequence of events. Some courts have rejected records dictated or written more than 30 days after the event.
- **Good records are accurate,** clear, precise and devoid of vagueness.
- **Good records are comprehensive,** including history, physical exam, lab reports, diagnosis, therapeutic plan, risks and alternatives, consent forms, consultant reports, prescriptions, correspondence, notes of conversations (by phone or in person), and all instances of patient failure to comply with medications, appointments or instructions.
- **Good records are objective,** with no unprofessional opinions or judgmental comments.
- **Good records are legible,** preferably handwritten clearly, but typewritten if clear handwriting is impossible. The only abbreviations should be standard hospital symbols.
- **Good records are consistent.** If the absence of a symptom is noted once, it must be noted consistently, lest failure to note be interpreted in court as failure to notice.
- **Good records are unaltered.** NEVER erase any entry. Never attempt to "supplement," "complete," or "clarify" after a lawsuit is suspected or served. Changes can be made by drawing one neat line through an inaccurate entry with the date and signature of time of amendment. Additional sheets can be used to document supplemental information. **Altered records can make a defensible case indefensible.**

Obviously, records alone are not enough. Good medicine is the first requisite to protect a physician from malpractice lawsuits.

Good Medicine

Much advice has been offered by risk managers as to **what constitutes good medicine.** Some of the most frequent suggestions are capsulated below:

- **Stay within your own area of expertise.** Don't become involved in specialized treatment unless you have been trained in that specific specialty.
- **Maintain good patient rapport.** Be professional, empathetic and courteous at all times.
- **Confirm diagnoses** with all available techniques.
- **Refrain from over-optimistic prognoses** or promises of perfect results.
- **No experimentation in treatment** should be permitted unless informed consent is given by the patient and there is reason to believe no harm will be done to the patient. Document all treatment.
- **Clear communications.** Avoid exclusively verbal orders to patients, to staff or to pharmacies. Follow up with written directions for patients to take with them and read at leisure, written policies for staff and written prescriptions for pharmacies. Make sure patients clearly understand the consequences of failure to comply with instructions or medications. Take extra care when drugs have similar names and check to be sure decimal points are in the correct place.

- **When persons of the opposite sex are examined,** a third person should be present.
- **X-rays should be taken** at all key stages of treatment of fractures, foreign bodies and dislocation.
- **Be sensitive** to potential patient dissatisfactions, and take steps to defuse the situation: counsel, consult, refer.
- **Consult without delay** if problems develop with either prognosis or patient. Urge concerned patients to get a second opinion.
- **Avoid abandonment** of patients. Always refer if you choose not to treat.

Informed Consent

As one knowledgeable risk manager observes, the last thing a physician wants or needs is a surprised patient. Nobody can guarantee perfect results every time, but every patient needs to know what imperfections are possible, so there are no surprises.

Make sure the patient understands all significant potential hazards and that the patient signs a consent form prior to procedures or surgery. In an emergency, when care is urgently needed and the patient is unable to communicate, consent is said to have been given by law. It is better, however, if a spouse or relative also gives consent. In all other cases, consent must be clear and preferably in writing, from the patient or from the parents of a minor.

Good Staff Support

Proper selection and supervision of staff is critically important to a physician's successful rapport with patients.

Office procedures for handling patients with courtesy and efficiency should be reviewed periodically, especially as they relate to setting appointments, waiting in the office and answering telephones.

All office equipment should be checked at periodic intervals for operational functioning. Staff operating the equipment should also be evaluated for skill and competence. Staff should enforce patient confidentiality and be careful of open doors and hallway chatting.

Staff can protect or doom a physician in court by casual comments regarding fault. **Staff should never admit fault to anyone.** Additionally, the physician's liability insurance should never be mentioned.

Finally, staff should be extremely discreet in collecting fees due the physician. Accounts should not be turned over to a collection agency unless the physician has reviewed the grounds for a possible lawsuit.

If a Lawsuit Is Filed

If a problem is detected or if a lawsuit is filed, **notify the insurance carrier immediately.** There is no penalty for early or even unnecessary notification, and the more time the insurance attorney has to prepare to protect you, the better the attorney can perform.

Physicians should follow the guidance of their insurance company attorneys, should never communicate directly with the plaintiff or the plaintiff's lawyer, (that's what your lawyer is paid to do), and above all, should never fancy themselves attorneys. Remember, the trial lawyers have a motto: he who represents himself has a fool for a client.

Beware the magic question! A medical malpractice defense attorney has a recurring nightmare. In the bad dream, the physician-client is being interviewed or deposed, and the interviewer asks, "Ordinarily, Doctor, this result doesn't occur if the physician uses reasonable care, right?"

"STOP! Don't answer that!" the defense attorney shouts, waking in a cold sweat. The physician has just been asked a question with a hidden legal implication—the wrong answer will devastate his defense.

If the physician answers "This result ordinarily does not occur," the physician has just testified as a medical expert against himself by saying the result does not usually occur except where reasonable care is lacking.

The physician-client has admitted guilt and the plaintiff no longer has to prove negligence.

The correct answer to the magic question is: "Although the result may not ordinarily occur, when it does it is most often due to the inherent risk of the procedure."

The Tenth Commandment

Finally, the practice of good medicine is best summed up in the ubiquitous, anonymous "tenth commandment of risk management": **Thou shalt practice medicine as thou wouldst like it practiced on thyself.**

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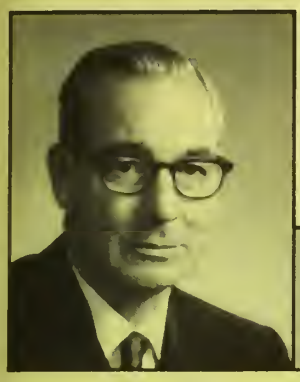

Schizoid

William B. McGrath, M.D.

The child who has experienced little or no comforting may later expect none for himself and have none to give to others. This will be the schizoid personality disorder. It is rather like an adult version of infantile autism.

The passive-aggressive is different in that he transacts with others, at least to the extent of harboring resentments and expressing them in covert ways. The inadequate is ingratiating, eager to please. Not so the schizoid. Only he, among the various personality disorders, actively seeks seclusion.

Solitude is like sensory deprivation: if too complete and prolonged it may engender a chronic undifferentiated schizophrenia. A person simply has to communicate. By default he may end up conversing only with himself and by way of delusions and hallucinations.

A model of the schizoid used to be the stumbling wino or the skinny drug addict. With the moral and social upheavals of recent years this no longer obtains. Drunks and addicts are not the loners of society anymore. Partly responsible are the professions of medicine and pharmacy and the amoral advertisers who popularize alcohol and mood-altering medicines and "recreational" drugs: antidepressants and amphetamines, tranquilizers, steroids, sleeping pills.

Schizoids are still to be found in hotels with linoleum floors and in all-night coffee houses among the "bag ladies" and the vagrants.

One must question the adage that "genius and madness are close allies." Very few schizoid artists (Van Gogh, for example) attain universal recognition. The musical and artistic creations of the majority are too eccentric, too peculiarly personal to be shared or to have appeal.

Schizoids relax only in the company of inanimate or nonhuman objects. They pore over their stamps or coins or collect cats. Or they tinker, once in a while coming up with worthwhile inventions. Warranting speculation is the pitiful story of the billionaire, Howard Hughes. Again, would not a one-dimensional diagnosis of addiction be meaningless?

Short of psychosis or certifiable deficiency the schizoids occupy the inner and outer limits of trait exaggeration. Over here may be a rigidly self-righteous prude, sneering at our imperfections. Over there may be a person so devoid of self-esteem that he would hesitate to impose his company on those around him.

They, the schizoids, do stay on the sidelines of cameraderie and competition. They have no fun. Good-natured teasing is taken too literally and they recoil from anything more intimate than the briefest handshake. (The quick retraction of the turtle's head into his shell is known as an Unken reflex.) Schizoids carry over in adult life the onanism of adolescence.

A very few schizoids will feign illness or actually hurt themselves, contriving to solicit care and kindness in a doctor's office or in a hospital.

The thought processes of the schizoid are oddly one-dimensional, concrete. A significant part of a mental status examination is the interpretation (abstracting) of proverbs. Asked what is meant by "A bird in hand is worth two in the bush," a schizoid replied: "Well, it would depend on what kind of birds."

It is not easy to give examples of schizoid persons. They seldom seek professional help and they do not socialize with us. It is like trying to describe a shadow, something without color or warmth or dimension. The schizoid hardly cares enough about himself to be fat, and we don't ever remember seeing one in a hurry. We do not really like or dislike these people because they neither like nor dislike us or themselves. They languish inside a cocoon of tepid narcissism.

It is imperative for parents or the family doctor or pediatrician or teacher to identify the schizoid

(Continued on page 12)

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Schizoid

(Continued from page 9)

personality disorder before it hardens into a permanent pattern.

The indolent child needs more than worming or a thyroid scan or a hearing aid. Someone should be actively concerned when a child spends too much time alone or in the bathroom or plucking hairs with tweezers. An alarm should sound if a youngster seldom smiles and does not welcome companionship or want to play. Some of these children are mired in misery, wondering inarticulately whether they will turn out to be homosexual.

Parental expectations in these cases must not be wishy-washy. A young couple, highly educated, brought in a youngster whose persistent thumb-sucking worried and embarrassed them. They had tried substitutes and repellants. They had interrogated and threatened and cajoled and bribed—all to no avail. The next time the lad started to suck his thumb, his outraged mother slapped his hand quite painfully and said, "Cut that out!" It worked.

A doctor's little boy began to stutter. The child was instructed to greet his father a dozen times with the words, "I hate you, you son of a bitch!" It worked. And the miraculous condiment of reciprocal mirth took away any real curse.

Personality disorders have their origin in the latency period. The schizoid youngster especially needs to participate in games or other activities involving his or her own sex, and some coercion may be justified: "Either go out for soccer or join the school band!" Parents should see to it that the girl has private time and shared interests with her mother, and the boy with his father. Even more firmly the parents ought to guide the endeavors and ingravescent expertise of one child in a direction practically opposite to that of his or her sibling. Too much family togetherness can be devastating.

Toward amateurish therapies for adults and the haranguing of inspirational or motivational programs we have sometimes expressed sarcastic skepticism.

But with play therapies and group and family participations, the specially trained psychiatrist or psychologist can be worth a great deal more than an orthodontist or a nutritionist in the treatment of an incipient schizoid personality disorder, commuting a life sentence of solitary confinement and regret. ■

William B. McGrath, M.D.

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Community Cancer Prevention

The best treatment of cancer is its prevention. Epidemiologic data collected in the last 25 years has convincingly suggested that over two-thirds of the incidence of human cancer can be explained by its association with a number of risk factors associated with lifestyle. Most prominent among these risk factors are smoking and diet, and in the Southwest, exposure to sunlight. Over the past decade a program has evolved at the College of Medicine which both provides service to the community and utilizes the community as a laboratory to conduct cancer prevention investigations.

An educational program about the prevention and early detection of skin cancer in Arizona was jointly initiated by Dr. Frank Meyskens of the Arizona Cancer Center and Dr. Michael Schreiber of the Tucson dermatologic community in 1980 and was designated the Arizona Sun Awareness Program (ASAP). The basic principles of prevention and early detection have been provided by this program to both lay and professional communities. This effort has been internationally recognized and we receive requests each week from around the world to help start up similar programs. The success of this program was important and has led to a fine working relationship between the Arizona Cancer Center and the broader medical and lay community.

Research emanating from laboratories at the College of Medicine and elsewhere has led to a major emphasis on Vitamin A and its natural and synthetic derivatives (retinoids). Subsequently two trials have been funded to see whether retinoids can prevent the development of skin cancer in humans. The first study deals with individuals at low risk for skin cancer. The subjects must have had removal of ten or more prior actinic keratosis (precursors to skin cancer) or one non-melanoma skin cancer. One half of the patients are randomized to receive a placebo and the other half to receive daily oral retinol (Vitamin A) at a low dose. Over 2,400 subjects will be required for this investigation and to date nearly 1,600 have been identified and randomized. The second investigation of non-melanoma skin cancer utilizes patients who have had documented removal of four or more non-melanoma cancers of the skin and therefore are at very high risk for a subsequent skin cancer. Over 400 subjects will be required and to date about 125 have been identified and randomized. This trial is a three arm study with the first two groups of patients receiving the types of intervention noted above, while a third group has been randomized to receive 13-cisretinoic acid (Accutane) at low dose. Accrual of subjects and patients to both of these investigations has been a statewide effort led by Drs. Norman Levine of the Department of Internal Medicine and Thomas Moon of the Department of Family and Community Medicine. The participation of the professional dermatology and lay community has been crucial to the initial success in accruing patients to these studies.

A second major effort has been in the area of colon cancer prevention. A considerable amount of epidemiologic and laboratory data suggests that increasing fiber or calcium in the diet decreases the risk for subsequent colon cancer. Preliminary investigations performed in the Green Valley retirement community has indicated that older individuals can be supplemented with a substantial amount of fiber without difficulty. Based on these investigations, a larger trial has been planned and will be conducted in the Sun City retirement community under the direction of Dr. David Alberts of the Department of Medicine. Subjects will be selected who are between the ages of 50 and 75 and have had a colon polyp removed within the prior 24 months. Our initial study will be a detailed investigation of the effect of fiber and calcium on biologic and biochemical bowel and bowel mucosa parameters. If this investigation is successful, a larger and more complex study will be performed which will involve all of

Maricopa County and northern Arizona. A second similar study led by Dr. David Earnest of the Department of Internal Medicine will use a pharmacologic inhibitor of bowel mucosal proliferation. These subjects will be recruited from Tucson and if the pilot study is successful, a larger trial is planned which will involve Pima County and southern Arizona.

A third major area of emphasis has been the prevention of cervical dysplasia. Based on a series of pilot investigations from 1980 to 1985, we established that retinoids can be used to reverse cervical preneoplasia. With the leadership of Dr. Earl Surwit of the Department of Obstetrics and Gynecology, we are conducting a randomized trial of topical retinoid acid versus placebo to determine the long term efficacy of this approach.

In the development of our community cancer prevention program we have established formal cancer prevention units in Tucson, Sun City, central Phoenix and Mesa. These have enhanced the activities and awareness of cancer prevention in geographic areas in which they have been established and will continue to do so in the future. Additional investigations involving other cancers will now be more easily developed and performed in the future. The establishment of this community based research program well demonstrates the possibilities for effective research in the community and establishes its feasibility. Hand-in-hand the academic, lay and professional community can plan together to study and conquer some of our most serious diseases. ■

Frank L. Meyskens, Jr., M.D.
Professor of Medicine
Associate Director for Cancer Prevention and Control
Arizona Cancer Center

Louis J. Kettel, M.D.
Dean, College of Medicine
Arizona Health Sciences Center

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Physicians in the News

William C. Scott, M.D.

William C. Scott, M.D., of Tucson has been elected vice-chairman of the American Medical Association's Council on Scientific Affairs for the 1987-88 year.

As vice-chairman of the council, Dr. Scott becomes chairman of DATTA, the Diagnostic and Therapeutic Technological Assessment Committee. DATTA is responsible for reviewing new medical procedures presented both by government and private sources, for analyzing the evaluating the efficacy of the new procedures and publishing their findings in the *Journal of the American Medical Association (JAMA)*.

Dr. Scott, a member of the council since 1984, was also re-elected to a second three-year term as a member of the council as well as being elected its vice-chairman.

A member of the Arizona delegation to the AMA House of Delegates since 1981, Dr. Scott served as an alternate AMA Delegate from 1977-80. He is a past president of the Arizona Medical Association (1975) and has been a member of ArMA's Board of Directors since 1969.

Associate Professor in the Department of Obstetrics and Gynecology at the University of Arizona College of Medicine since 1971, Dr. Scott served as chief of staff at University Hospital from 1977 to 1984, and has been medical director at University Medical Center since.

Dr. Scott has been a member of AMA's residency review committee in obstetrics and gynecology since 1981, is a member of the AMA Section Council on Ob-Gyn, and served as chairman of ArMA's Maternal and Child Health Care Committee from 1976-84. A former Chairman of the Arizona Chapter of the American College of Obstetrics and Gynecology (ACOG), he just completed a three-year term as chairman of District VIII ACOG, the 14-state western region.

A graduate of the Medical College of the University of Colorado, Dr. Scott interned at the U.S. Naval Hospital, Great Lakes, Illinois, and at the University of Colorado . He completed residencies at St. Joseph's Hospital and Colorado General Hospital in Denver.

Dr. Scott is Board certified and a fellow of the American College of Obstetrics and Gynecology, the American College of Surgeons, and the Pacific Coast Obstetrics and Gynecological Society. He is a member of the Southwestern Surgical Congress, the Central Association of Ob-Gyn, the Southwest Ob-Gyn Society, the American Society of Cytology, the American Society of Colposcopy and the Association of Professors of Ob-Gyn.

James E. Campbell, M.D.

James E. Campbell, M.D., has been appointed medical director of Charter Hospital of Glendale, which offers psychiatric and addictive disease programs for all ages.

Campbell, who has been in private practice in the Phoenix area since 1971, is certified by the American Board of Psychiatry & Neurology. He is president of the Phoenix chapter of the American Academy of Child and Adolescent Psychiatry and has served as president of the Arizona Psychiatric Society. He also is co-author of the book "Rapid Relief from Emotional Distress."

Campbell received his medical degree from St. Louis University Medical School and served a general psychiatric residency and medical internship at Michael Reese Hospital in Chicago.

Charter Medical Corporation owns and operates 85 hospitals worldwide; the majority are full-service psychiatric hospitals. Charter Hospital of Glendale is located at 6015 W. Peoria.

Jeffrey Edelstein, M.D., recently completed the first phase toward acceptance as a member of the American Society of Ophthalmic Plastic and Reconstructive Surgeons (ASOPRS) with the society's approval of his thesis, "Medial Palpebral Tendon Repair for Medial Ectropion of the Lower Eyelid."

The society consists primarily of ophthalmologists who have a special interest in cosmetic and reconstruction eyelid surgery. Membership requirements include completion of an approved fellowship in ophthalmic plastic surgery, writing an acceptable thesis, and successfully completing oral and written examinations. To be accepted by ASOPRS, the thesis must involve an original, indepth look at a new topic or challenge an existing topic.

Dr. Edelstein's paper dealt with a new procedure to correct medial ectropion, or an everted malposition of the nasal eyelid, usually caused by trauma, cancer or a birth defect. In severe cases, the treatment of choice has been transnasal wiring, which anchors both medial canthi together with the passage of a wire through the nasal bones. Although effective, transnasal wiring is an extremely invasive procedure.

The procedure described in Dr. Edelstein's thesis utilizes a periosteal flap left attached to the posterior lacrimal crest to anchor the medial eyelid into position rightly against the eyeball.

His paper explains that the medial palpebral tendon reconstruction with a periosteal flap can be used when the lower eyelid malposition is primarily medial and less complex procedure cannot adequately correct the abnormality. The procedure is designed to replace a dehiscence of the deep attachments of the medial orbicularis muscle with strong autogenous tissue directed toward to posterior lacrimal crest.

Dr. Edelstein's paper reviewed surgeries in which medial palpebral tendon reconstruction was performed on seven lower eyelids with medial instability or ectropion and a dehiscence of the medial palpebral tendon. After a mean follow-up of seven months, 86 percent of th eyelids had acceptable cosmetic and functional results.

The use of the periosteal flap to replace a dehisced medial palpebral tendon has several advantages, according to Dr. Edelstein's research. The periosteum is strong autogenous tissue. The medial canthal angle can be preserved. The normal tarsal glands are saved and a lid notch is avoided. The medial canthal support is achieved without violating bone, which can be particularly important for reconstruction after tumor excision. In addition, the medial palpebral tendon reconstruction may avoid or delay skin grafting in patients with mild cicatricial ectropion.

ASOPRS, founded in 1969, is a specialty society dedicated to excellence in cosmetic and reconstructive eye plastic surgery. During its 18-year existence, it has grown to include approximately 250 members throughout the U.S. According to Dr. Edelstein, many recent advances in this field are directly related to a greater awareness and application of anatomic concepts developed by many of the members of the society.

Following acceptance of his thesis, Dr. Edelstein was scheduled to take the written and oral exams for membership in the society in November.

Dr. Edelstein moved his practice from Tucson to Mesa this year. He is Board certified, a member of the American Academy of Ophthalmology and a graduate of the Medical College of the University of Wisconsin. He completed his residency at the Henry Ford Hospital in Detroit and a fellowship with R. M. Dryden, M.D., at St. Joseph's Hospital, Tucson. He currently has staff privileges at Desert Samaritan, Mesa Lutheran, St. Luke's, and other Phoenix area hospitals.

Joseph W. Hanss, Jr.,M.D.

Joseph W. Hanss, Jr., M.D., has been elected Chairman of the Arizona Chapter of the American College of Obstetrics and Gynecology (ACOG). Dr. Hanss, from Phoenix, succeeds Tucson obstetrician James Blute, III, as Chairman of Arizona ACOG.

Dr. Hanss, incumbent Secretary of the Arizona Medical Association, had served as Vice Chairman of Arizona ACOG during the past three years while Dr. Blute was chairman. He was elected chairman during the District VIII (western region) ACOG meeting in San Francisco.

During the past five months, Dr. Hanss has been extremely active in promoting public awareness of the potentially disastrous results of the liability lawsuit crisis on the members of the medical community, particularly high-risk specialists such as ob-gyns. A recent Arizona ACOG membership survey showed forty percent are planning to drop obstetrical services within three years, either by limiting their practices to gynecology, leaving the state or retiring altogether. As a member of the Governor's task force on the liability crisis, Dr. Hanss brought this information and high-risk physicians' concerns about the growing personal pressures related to the liability crisis to the attention of state officials.

During his three-year term, he plans to continue his efforts to promote public awareness of the consequences of an unresolved tort crisis in Arizona, and to work toward solutions.

Dr. Hanss, a graduate of the Medical College of the University of Buffalo, interned and completed his residence in obstetrics and gynecology at the Genesse Hospital, Rochester, New York. He is Board certified and has staff privileges at Good Samaritan, St. Joseph's, Phoenix Memorial and other Phoenix-area hospitals. He is a past chairman of the ob-gyn department at Good Samaritan, and a past president of the Phoenix Ob-Gyn Society.

Janice B. Dorn, M.D., Ph.D., has become the host of two separate ongoing radio shows in the Phoenix area.

Dr. Dorn, a psychiatrist, answers listeners' questions on an open variety of mental health topics of interest each Friday on the Phoenix Christian radio station KHEP-AM from 12:35 to 1:00 p.m.

Every other Friday morning, from 10:00 to 11:00 a.m., she discusses a specific topic of public interest with veteran talk show host Pat McMahon on KTAR-AM. Topics covered on the KTAR show include obsessive love, transsexuals, light affective disorders, and cocaine addiction. Calls from listeners are also answered on the KTAR show.

Dr. Dorn, who is in private practice in Phoenix, earned her Ph.D. in neuroanatomy at the Albert Einstein College of Medicine, and subsequently was an Associate Professor of Anatomy and Physiology at the Chicago Medical School. She was graduated from the University of Juarez Medical School in Mexico and interned in neuropsychiatry at the University of Juarez Medical School in Mexico and interned in neuropsychiatry at the University of New Mexico Medical Center. She completed a residency in anesthesiology at the UCLA Medical Center, where she also completed a fellowship in cancer pain management. She completed her psychiatric residency at the Maricopa Medical Center in Phoenix.

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State Receives Funding For AIDS Prevention

The Arizona Department of Health Services has announced it will be receiving an additional $164,000 in Federal funding for AIDS prevention and control during the current fiscal year. The award from the Centers for Disease Control (CDC) will be used to expand AIDS-related services through local health departments and initiate new programs for minority groups.

An amount of $261,000 of the additional funding will supplement current AIDS counseling and testing programs in Maricopa and Pima Counties, including activities specifically planned for family planning, prenatal, and sexually transmitted disease clinics. It will also provide for initiating new programs for counseling, testing and education in Cochise, Coconino, Pinal and Yuma Counties.

AIDS health education and risk reduction programs for the general public and high risk groups in Maricopa and Pima Counties will receive $69,000 of the award.

New funding of $125,000 will be used to develop AIDS health education programs for Arizona's minority populations. The project will gather baseline data on the knowledge, attitudes and beliefs of Arizona's Black, Hispanic and Native American populations regarding AIDS. Money will be provided to minority organizations for the development of culturally sensitive and appropriate education programs.

Funding in the amount of $159,000 will cover the cost of drugs for AIDS. This money is targeted at individuals who are neither eligible under the Arizona Health Care Cost Containment System (AHCCCS), nor covered by third party insurance.

"This additional funding will give our efforts a significant boost in fighting a major public health problem. We will be able to initiate new services in four additional counties while expanding planned education programs for the general population, high risk groups and minorities," stated Ted Williams, Director of the Arizona Department of Health Services.

The $614,000 from CDC will be added to the current $814,000 in State and Federal funding for AIDS prevention and control administered by the Arizona Department of Health Services.

Smoking and Oral Contraceptive Use

Women who smoke and use oral contraceptives (OCs) are at increased risk of heart attack, but smoking is the greater risk factor of the two, a study in a recent *Journal of the American Medical Association* says. Gary M. Goldbaum, M.D., now of the Thurston County, Washington, Health Department, and colleagues at the Centers for Disease Control, Atlanta, reached the conclusion by comparing data from a national health risk factor survey with data on non-fatal heart attacks among U.S. women in 1982. For that year, they estimate, more than 3,000 non-fatal heart attacks among women aged 35 to 44 years might have been prevented if women neither smoked nor used OCs. But because of its high prevalence, smoking—regardless of OC use status—was the major risk factor, they say. While nonsmokers who used OCs accounted for 7.5 percent of these "excess" heart attack cases, they note, smokers who did not use OCs accounted for 75.4 percent. "Therefore, health care providers need to intensify their efforts to reduce smoking among their patients," the authors conclude.

Autopsy Legislation Around The World

Declining autopsy rates are an international problem, says a report in September's *Archives of Pathology and Laboratory Medicine*. The report, by Einar Svendsen, M.D., Ph.D., of the University of Bergen, Norway, and Rolla B. Hill, M.D., a private practitioner in Philo, California, reviewed information on autopsy laws, regulations, rates and practice in 29 industrialized nations. Laws in many countries have been revised in recent years, introducing more restrictive rules, with consent required from next-of-kin, the study finds. With one exception—Finland—introduction of a requirement for consent was followed by a decline in the autopsy rate, the authors report. "In view of the importance of autopsy to society, an international effort to educate the public and increase autopsy utilization is imperative," the report concludes.

Genetic Factors In Skin Disease

Two studies in September's *Archives of Dermatology* suggest a genetic link in the development of two serious skin problems. In the first study, Christoph Luderschmidt, M.D., of the Rheinische

Friedrich-Wilhelms University, Bonn, West Germany, and colleagues conducted genetic analyses on 136 patients with progressive systemic scleroderma, a chronic hardening and thickening of the skin. They found that several genes linked to human leukocyte antigen (HLA), a cell surface protein, appear to control a patient's susceptibility to the disease, with different genes associated with different aspects of the disease. In the second study, Jean-Claude Roujeau, M.D., of the Hospital Henri Mondor, Creiteil, France, and colleagues, performed similar HLA typing in 44 patients suffering from toxic epidermal necrolysis (TEN), severe blistering often caused by drug reactions. Different HLA-linked genes were found to be associated with different drug-related cases of TEN, the researchers report.

Smoking and Oxygen Don't Mix

A letter in a recent *Journal of the American Medical Association* shows why one should heed warnings against smoking near oxygen equipment in hospitals. Glenn William Knox, M.D., and Mary Ann Smith Frable, M.D., of the Medical College of Virginia, Richmond, describe three men aged 51 to 64 years who suffered severe burns of the lining of their noses as a result of smoking cigarettes while being administered oxygen via a nasal tube. All three had a history of alcohol and substance abuse. Preventing this kind of injury "is not only the responsibility of the patient, but of the administrative, nursing and physician staffs as well," the authors say, noting underlying psychiatric disorders, substance abuse or senility can increase the problem. Smoking should be permitted only in designated hospital areas; "patients should be educated in this regard and rules limiting smoking enforced," they say.

Vitamin A Deficiency Test

Vitamin A deficiency among young children in developing countries causes blindness and can lead to other illness. Direct serum vitamin A measurement in such settings is difficult, but a study in September's *Archives of Ophthalmology* says a simple, reliable test may now be available to identify children at risk by detecting mild xerophthalmia, the "dry-eye" problems seen with vitamin A deficiency. Gantira Natadisastra, M.D., of the University of Padjajaran, Bandung, Indonesia, and colleagues at the Johns Hopkins Hospital, Baltimore, used the test, impression cytology, to study 75 Indonesian children with mild xerophthalmia and 75 normal controls. Impression cytology involves non-traumatic sampling and analysis of cells from the outer eye surface. Results, which were closely correlated with baseline serum vitamin A levels, gauged improvement in affected children after vitamin A therapy. The test also spotted pre-clinical abnormalities in a significant percentage of controls and documented post-treatment improvement.

Psychiatric Disorders Among Children

A study in September's *Archives of General Psychiatry* on emotional and behavioral problems among children in Canada indicates that despite high overall prevalence of various disorders, relatively few affected children are receiving specialized mental health services. David R. Offord, M.D., of Chedoke-McMaster Hospitals, Hamilton, Ontario, and colleagues studied the prevalence of four problems—conduct disorder, hyperactivity, emotional disorder and somatization in children in some 1,900 Ontario households. Among children aged 4 to 16 years, the overall prevalence rate of one or more disorders within the six months prior to the study was 18 percent, yet only one in six of these children received mental health or social services in that six-month period. The prevalence of hyperactivity and one or more disorders were significantly higher in urban areas than rural areas.

Suramin Not Recommended As AIDS Therapy

The drug suramin has exhibited in vitro activity against the human immunodeficiency virus (HIV), but cannot as currently administered be recommended as an effective therapy for AIDS, concludes a multi-center study reported in a recent *Journal of the American Medical Association*. Suramin, long-used for treatment of a pair of parasitic diseases, gained attention as a potential AIDS drug because it inhibits reverse transcriptase, which HIV depends upon for replication and infectivity. The newly reported study, by Bruce D. Cheson, M.D., of the National Cancer Institute, Bethesda, Maryland, and colleagues at eight other medical centers, involved 98 AIDS patients given suramin for up to one year. The authors say the drug exhibited moderate anti-HIV activity, but this "did not appear to be associated with clinical response or immunologic improvement."

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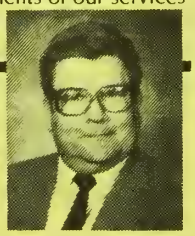

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Clinical Investigation

Low Blood Mononuclear Cell Magnesium Content and Hypocalcemia in Normomagnesemic Patients

ELISABETH RYZEN, MD; TONY A. NELSON, MD, *and* ROBERT K. RUDE, MD, *Los Angeles*

Hypomagnesemia can cause hypocalcemia. Because less than 1% of the total body magnesium (Mg) is in extracellular fluids, however, patients may be Mg-deficient despite normal serum Mg concentrations. To determine if hypocalcemia can be seen in patients who have normal serum Mg concentrations but low intracellular Mg, we studied the serum and mononuclear cell Mg contents in 82 alcoholic subjects, 30 of whom had hypocalcemia that could not be explained by other known causes of hypocalcemia. The mononuclear cell Mg content in both hypomagnesemic and normomagnesemic patients with and without hypocalcemia was significantly lower than in normal controls. The serum Mg level did not correlate with the mononuclear cell Mg or serum calcium level, but hypocalcemic patients had a significantly lower mononuclear cell content than normocalcemic patients. Six patients underwent parenteral Mg tolerance testing as an additional measure of Mg deficiency and had increased Mg retention. The serum calcium concentration returned to normal in hypocalcemic patients who were given magnesium intravenously.

(Ryzen E, Nelson TA, Rude RK: Low blood mononuclear cell magnesium content and hypocalcemia in normomagnesemic patients. West J Med 1987 Nov; 147:549-553)

Hypomagnesemia is a common clinical finding.[1,2] Causes of magnesium (Mg) deficiency include the malabsorption syndromes, diarrhea, diabetes mellitus, alcohol abuse, hypophosphatemia and therapy with loop diuretics, aminoglycosides or a saline solution given intravenously. Many patients with hypokalemia, hypophosphatemia and hyponatremia also have hypomagnesemia.[3] Hypomagnesemia may result in hypocalcemia due to impaired parathyroid hormone release or skeletal and renal resistance to parathyroid hormone action.[4-8]

Low serum Mg concentrations usually reflect Mg depletion in tissues.[9,10] But tissue Mg deficiency can be seen even in the presence of normal serum Mg concentrations.[9,11-16] The clinical significance of normomagnesemic Mg deficiency is unclear, but some studies have described clinical complications known to be associated with Mg deficiency in patients with normal serum Mg concentrations. Mg supplementation in such cases resolved clinical problems such as hypocalcemia,[6,17] cardiac arrhythmias[14] and refractory hypokalemia.[16]

Although a single ideal test for assessing Mg deficiency has not yet been found,[18] one study suggested that bone Mg is the best measure of body Mg stores.[10] Measuring bone Mg is not practical clinically, however. Magnesium can also be measured in peripheral blood mononuclear cells, which are more readily accessible than bone. The mononuclear cell Mg content has been reported to be reduced in patients with reduced bone Mg content[19] and in normomagnesemic patients at risk for Mg deficiency.[13-15]

We have observed normomagnesemic patients at risk for Mg deficiency who manifest hypocalcemia that could not be explained by known causes of hypocalcemia such as hypoalbuminemia, renal failure and acute pancreatitis. To help assess if patients with "unexplained" hypocalcemia are Mg deficient despite normal serum Mg concentrations, we determined their mononuclear cell Mg content.

Study Design and Methods

Patients and Controls

Alcohol abuse is a known risk factor for Mg deficiency.[9,11,12,19,20] We therefore studied alcoholic patients admitted to the general internal medicine service of the Los Angeles County-University of Southern California Medical Center. Admitted patients' charts were screened for alcoholism an average of two mornings per week over an 18-month period. Patients with renal failure (serum creatinine > 1.5 mg per dl), acute pancreatitis, hypoparathyroidism and other known causes of hypocalcemia other than Mg deficiency were excluded (Table 1).[21] Patients who had already received Mg therapy were also excluded from study. A total of 82 patients were studied. Admission diagnoses included alcohol intoxication or withdrawal syndrome, pneumonia, cellulitis, gastritis, alcoholic liver disease, placement problems and combinations of the above. None of the patients had symptoms that could be attributed exclusively to Mg deficiency or to hypocalcemia. All but five of the patients, however, had nonspecific symptoms such as weakness, seizures and cardiac arrhythmias in which Mg deficiency or hypocalcemia could not be excluded as contributing factors.

Normal healthy volunteers (medical students and em-

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ABBREVIATIONS USED IN TEXT

Mg = magnesium
PBS = phosphate-buffered saline

ployees of the clinical research center) served as a control population. In our laboratory, we have previously not found any relation of mononuclear cell Mg content to age or sex in healthy subjects and therefore did not age- and sex-match our volunteer control subjects.

Protocol

Fasting morning blood specimens were drawn on all patients within 24 hours of admission to measure serum Mg, calcium, albumin and creatinine concentrations and the mononuclear cell Mg content. To further assess the presence of Mg deficiency, after informed consent was obtained, six patients also underwent low-dose parenteral Mg tolerance testing at the Clinical Research Center, as previously described.[22] A baseline spot urine test was done for Mg and creatinine. Then 0.2 mEq (2.4 mg) elemental Mg per kg lean body weight was infused as a 50% solution of magnesium sulfate in 50 ml dextrose and water over four hours. All urine was collected for 24 hours, starting with the infusion, to measure Mg and creatinine concentration. The percentage of Mg retained was calculated using the following formula:

$$\%\ \text{Mg retained} = 1 - \left[\frac{\text{Postinfusion urine Mg}}{(\text{preinfusion urine Mg/Cr} \times \text{postinfusion urine Cr})}\right] \times 100,$$

$$\text{total elemental Mg infused}$$

with Cr meaning creatinine content.

A total of 21 hypocalcemic patients (10 with hypomagnesemia, 11 with normomagnesemia) received 32 to 64 mEq elemental Mg per day by constant intravenous infusion for three to five days. Mg tolerance testing was repeated on four of these patients three days after the Mg therapy was completed.

Methods

Serum and urine Mg levels were measured by atomic absorption spectrophotometry. Serum calcium, creatinine and albumin concentrations were measured by an AutoAnalyzer.

The mononuclear cell Mg content was measured using a modification of methods previously described.[13,23] Heparinized blood (10 to 15 ml) was mixed with an equal volume of phosphate-buffered saline (PBS) solution at pH 7.4, containing sodium chloride, 8.1 grams per liter (0.14 mol per liter); dibasic sodium phosphate, 1.22 grams per liter, and sodium biphosphate in water, 0.194 grams per liter. Twenty ml of Ficoll-Hypaque (Pharmacia Fine Chemicals) was then layered below the blood and PBS solution using a 20-gauge spinal needle and the preparation was centrifuged at 400 × g for 35 minutes. The mononuclear cell layer was collected from the Ficoll-Hypaque-plasma interface, washed with 10 ml PBS solution and centrifuged at 600 × g for ten minutes. The supernatant was then discarded and the pellet washed in another 10 ml PBS solution and centrifuged at 600 × g for ten minutes. The wash was repeated and the remaining pellet brought up in 1 ml distilled water and stored at −20°C until time of assay. Before the assay, the cells were thawed and lysed by sonication using a Heat Systems Ultrasonic Sonicator. The lysate was then centrifuged at 1,500 revolutions per minute for ten minutes to remove cellular debris. The Mg content of the lysate was measured by atomic absorption spectrophotometry. Lysate protein was measured by the method of Lowry.[24] In our laboratory, intraassay and interassay variability for lysate Mg content is 5% to 10%.

Statistics

The mean values of two groups were compared using the Wilcoxon non-paired ranked sum test, as the data were not normally distributed.

Results

In all, 36 of the 82 patients had hypomagnesemia (serum Mg < 1.7 mg per dl, mean 1.31 ± 0.04 [mean ± standard error of the mean]) and 46 had normomagnesemia (serum

TABLE 1.—*Causes of Hypocalcemia*

Hypoalbuminemia
Renal failure
Magnesium deficiency
Primary hypoparathyroidism
Pseudohypoparathyroidism
Acute pancreatitis
Massive transfusions with citrated blood
Hypermagnesemia (therapy for eclampsia)
Vitamin D deficiency
Osteoblastic tumor metastases
Hungry bone syndrome
Postthyroidectomy hypocalcemia
Rhabdomyolysis
Hyperphosphatemia

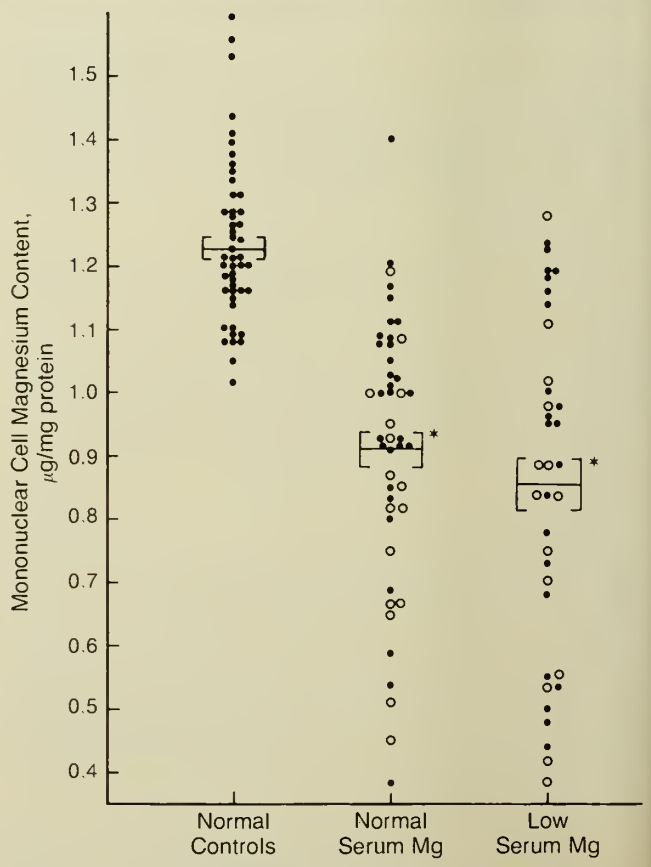

Figure 1.—Mean mononuclear cell magnesium (Mg) content in normal controls and in normomagnesemic and hypomagnesemic patients. ∗ $P < .001$ compared with normal controls. Open circles indicate hypocalcemic patients.

TABLE 2.—*Serum Magnesium (Mg) and Calcium Concentrations and Mononuclear Cell Mg Content in Hypomagnesemic and Normomagnesemic Patients*

Patient Features	*Serum Mg, mg/dl*	*Mononuclear Cell Mg, μg/mg*	*Calcium, mg/dl**
Low serum Mg, low serum calcium (N=14)	1.26±0.1	0.79±0.1†	8.0±0.1 (range 7.2-8.4)
Normal serum Mg, low serum calcium (N=16)	1.98±0.1	0.83±0.1†	8.0±0.1 (range 7.5-8.4)
Low serum Mg, normal serum calcium (N=22)	1.34±0.1	0.89±0.1†	8.8±0.1 (range 8.5-9.1)
Normal serum Mg and normal serum calcium (N=30)	1.94±0.1	0.96±0.1†	9.0±0.1 (range 8.5-10.3)

*Serum calcium has been corrected 0.8 mg per dl for every 1 gram per dl deviation from the mean normal serum albumin level of 4 grams per dl (from Broadus[25]).

†$P<.001$ compared with normal controls, 1.23±0.02 μg Mg per mg protein (mean±standard error of the mean).

Mg ≥ 1.7 mg per dl, mean 2.0±0.04). The mononuclear cell Mg levels in both groups of patients are shown in Figure 1 compared with normal controls. The mononuclear cell Mg content in the hypomagnesemic patients was 0.86±0.04 μg Mg per mg protein, significantly lower than in normal controls (1.23±0.02 μg Mg per mg protein, $P<.001$). Of even greater interest is the finding that the normomagnesemic patients also had a significantly reduced mononuclear cell Mg content compared with normal controls (mean = 0.91±0.03 μg per mg, $P<.001$). The mononuclear cell Mg content in hypomagnesemic patients was not significantly lower than in normomagnesemic patients. The serum Mg concentration did not correlate with the mononuclear cell Mg content.

The serum Mg level also did not correlate with the serum calcium concentration. A total of 14 of the 36 hypomagnesemic patients (39%) and 16 of the 46 normomagnesemic patients (35%) had hypocalcemia (corrected serum calcium <8.5 mg per dl) that could not be explained by hypoalbuminemia or clinical diagnoses known to cause hypocalcemia (Table 1).[21] The mean mononuclear cell Mg content of all hypocalcemic patients was significantly lower than the mononuclear cell Mg content of all normocalcemic patients (0.81 μg Mg per mg protein and 0.93 μg Mg per mg protein, respectively, $P = .018$; Wilcoxon non-paired ranked sum), but only a weak correlation was seen between the mononuclear cell Mg content and serum calcium level ($r = .26$, $P = .02$). Table 2 summarizes the serum Mg, serum calcium and mononuclear cell Mg contents in the different patient groups. Both hypomagnesemic and normomagnesemic hypocalcemic patients had mean mononuclear cell Mg content significantly lower than in normal controls. Of the 16 normomagnesemic, hypocalcemic patients, 14 (88%) had a mononuclear cell Mg content lower than that of the lowest normal control (Figure 1). The mononuclear cell Mg content in the hypomagnesemic, hypocalcemic patients was not significantly lower than in the normomagnesemic, hypocalcemic subjects.

Table 3 shows the mononuclear cell Mg content and retention of Mg in the patients who also underwent parenteral Mg tolerance testing. The serum creatinine concentrations in these patients were normal (0.95±0.04 mg per dl). All patients had significantly greater than normal Mg retention at 24 hours in addition to a low mononuclear cell content (normal Mg retention = 0% to 30%).

Magnesium retention normalized in the four patients who underwent repeat Mg tolerance testing after Mg supplementation. The mononuclear cell Mg content, however, increased in only three of six patients tested after five days of intravenous Mg therapy.

The serum calcium level returned to normal in the 10 hyponagnesemic and 11 normomagnesemic, hypocalcemic patients who received 32 to 64 mEq of elemental Mg per day by continuous intravenous infusion for three to five days after admission. Figure 2 shows the admission and post magnesium therapy corrected serum calcium values in the 11 normomagnesemic, hypocalcemic patients. The serum Mg level remained within the normal range during therapy.

Discussion

Hypomagnesemia is seen in about 10% of all patients admitted to public hospitals[2,26,27] and in as many as 65% of patients in medical intensive care units.[17] The clinical consequences of Mg deficiency other than hypocalcemia can include cardiac arrhythmias,[14,16,28,29] potassium wasting[16,29,30] and neuromuscular abnormalities.[31] These are reviewed elsewhere.[1,32,33]

Less than 1% of the total body Mg is in the extracellular space. Therefore, the serum Mg concentration may not be an accurate measure of intracellular Mg stores. Dehydration, hypoxia, acidosis and tissue breakdown may result in a rise of the serum Mg concentration into the normal or even elevated range despite depleted body stores.[9,34(p361)] Although low serum Mg levels usually indicate a depletion of Mg in tissues,[10] Mg deficiency can be present even with normal serum

TABLE 3.—*Data on Patients Who Underwent Parenteral Magnesium (Mg) Tolerance Testing**

Patient		*Serum Mg, mg/dl*	*Mononuclear Cell Mg, μg/mg*	*Serum Calcium, mg/dl*	*Retention at 24 h, %*
1	Before	1.9	0.93	8.0	64
	After	2.0	0.94	9.3	0
2	Before	1.8	0.90	8.3	82
	After	1.9	1.19	9.2	5
3	Before	1.9	0.75	8.0	72
	After	1.9	0.79	9.0	..
4	Before	1.9	0.87	8.0	65
	After	2.1	0.90	8.9	..
5	Before	1.1	0.68	9.3	95
	After	2.1	0.90	9.2	10
6	Before	0.9	0.96	9.1	80
	After	1.9	1.21	9.4	0
Normal		1.7-2.1	1.11-1.35 (mean±SD)	8.5-10.3	0-30 (mean±2SD)

SD=standard deviation

*On all patients, values shown are those obtained before and after 3 to 5 days of intravenous administration of magnesium sulfate, 32 to 64 mEq per day.

Mg values. This has been shown using measures of muscle Mg,[9,11,12] Mg balance studies,[9,11,20] parenteral Mg tolerance testing[9,11,20,22] and the mononuclear cell Mg content,[13-15] and is confirmed by our findings in this study.

The incidence and significance of normomagnesemic Mg deficiency have not been well studied because of the practical difficulty of assessing Mg depletion in normomagnesemic patients. Cardiac arrhythmias responsive to Mg therapy have been reported in normomagnesemic patients with low lymphocyte Mg contents.[14] Impaired parathyroid hormone release in a normomagnesemic, hypocalcemic patient has been reported in one patient whose calcium level returned to the normal range with Mg therapy.[6] We have also previously reported the cases of two normomagnesemic, hypocalcemic patients whose calcium levels returned to normal with Mg therapy,[17] but no measures of intracellular Mg were done to confirm the presence of Mg deficiency. About 22% of hypocalcemic patients have been reported to have overt hypomagnesemia.[3] In our study, 87% of the normomagnesemic patients with "unexplained" hypocalcemia had a low mononuclear cell Mg content, and their serum calcium concentrations returned to normal with Mg therapy. Therefore, our data show that patients with unexplained hypocalcemia who are at risk for Mg deficiency have a high probability of being Mg deficient even if the serum Mg concentrations are normal. Our findings also suggest that intracellular Mg deficiency may play a role in the pathogenesis of the hypocalcemia in these patients.

Other evidence for Mg deficiency in these normomagnesemic patients is provided by the data in the subgroup of patients who underwent parenteral Mg tolerance testing as an additional measure of Mg deficiency. In the presence of Mg deficiency, patients retain greater than normal amounts of parenterally administered Mg loads.[11,18,20] The patients in this study also showed increased Mg retention that resolved after Mg therapy, findings that are highly suggestive of Mg depletion.

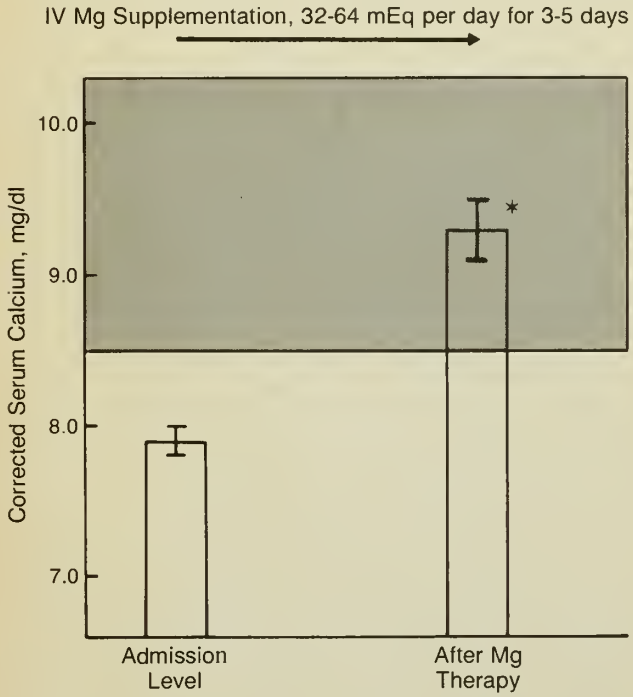

Figure 2.—Corrected serum calcium concentration in normomagnesemic patients with unexplained hypocalcemia before and after magnesium (Mg) supplementation therapy (N = 11). The shaded area indicates the normal range. $*P<.001$ compared with normal controls.

The mononuclear cell Mg content did not consistently increase with Mg therapy despite resolution of the hypocalcemia and normalization of Mg retention. This may reflect the long life span of mononuclear cells,[35(p247)] whose measured Mg content may lag behind acute clinical changes in Mg status and may not reflect rapid changes in the Mg content of the parathyroid glands, bone and kidney. This is further shown by the finding of a normal mononuclear cell Mg content in several hypomagnesemic patients. Thus, measures of the mononuclear cell Mg content alone may not be 100% sensitive or specific in the diagnosis of Mg deficiency in individual patients and may need to be interpreted with caution in patients experiencing rapid Mg losses or in those who have received Mg supplementation previously. The amount of time required to definitively alter the mononuclear cell Mg content after Mg repletion or depletion occurs is unclear.

In our patients, hypocalcemia in normomagnesemic patients was statistically as common as in hypomagnesemic patients (35% and 39%, respectively). Although the degree of hypocalcemia in most of these patients was mild, these findings indicate that in any given patient with Mg deficiency, some factor other than the degree of hypomagnesemia mediates the development of hypocalcemia. Our data show significantly lower mononuclear cell Mg contents in hypocalcemic patients than in normocalcemic patients and suggest that the intracellular Mg content may be more important than the serum Mg concentration in determining in which patients hypocalcemia will develop. Although we also saw a statistically significant correlation between the mononuclear cell Mg content and serum calcium levels, the correlation was weak. Therefore, other factors need to be considered. One study has shown that only a small portion (2%) of intracellular Mg is rapidly exchangeable, the rest being bound in intracellular organelles.[36] Thus, it is possible that free cytoplasmic Mg in the parathyroid glands or in the parathormone end-organ-responsive tissues, bone and kidney, is preferentially lowered in those patients in whom hypocalcemia develops. This may also explain why a rise in the total mononuclear cell Mg content is not seen in some patients after several days of Mg therapy despite resolution of the hypocalcemia and return of parenteral Mg tolerance to normal. Measuring the mononuclear cell Mg content using different techniques[37] might also help distinguish those patients in whom hypocalcemia develops from those in whom it does not.

Other possible causes of hypocalcemia other than Mg deficiency are summarized in Table 1 and discussed elsewhere.[21] Hypoalbuminemia is the most common cause of "false" hypocalcemia. For this reason, in this study we adjusted all measured total serum calcium concentrations for changes in the serum albumin concentration.[25(p1007)] The accuracy of formulas used to correct the serum calcium value for the albumin concentration is controversial,[38-40] and it is possible that measures of ionized calcium would yield different results. Renal failure, the most common cause of true hypocalcemia, was not present in our patients, and most of the other diagnoses listed in Table 1 other than Mg deficiency were also easily excluded clinically in our study population. Some of our patients may have had vitamin D deficiency, as alcoholism and liver disease have been associated with low total 25-hydroxycholecalciferol (vitamin D) concentrations.[41] Hypocalcemia due to vitamin D deficiency, however, would not have rapidly

corrected with Mg therapy and the small amounts of vitamin D that are present in patients' hospital diets. Although parathyroid hormone concentrations were not measured, primary hypoparathyroidism was excluded based on the absence of hyperphosphatemia and the normalization of serum calcium levels with Mg supplementation alone. Immunoreactive parathormone concentrations in Mg-deficient patients have been reported to be low, normal or high.[4-8]

Some authors have reported an association of hypocalcemia with sepsis, stress and critical illness.[42,43] The mechanism for hypocalcemia in such patients is unclear, however, and the status of body Mg stores was not assessed. Thus, although some of our patients suffered from infections and were under stress, we cannot explain their hypocalcemia on that basis alone and must consider what role their intracellular Mg deficiency may have played.

Finally, even though these patients had evidence of intracellular Mg depletion, it is possible that this was unrelated and incidental to their hypocalcemia and an as-yet-unidentified factor may have been responsible for the hypocalcemia. The resolution of the hypocalcemia may have occurred independent of Mg supplementation. Thus, further studies using varying degrees of Mg restriction and supplementation are needed before the resolution of the unexplained hypocalcemia in these patients could be attributed solely to Mg supplementation.

In summary, our data show that intracellular Mg depletion in the presence of normal serum Mg concentrations is a common finding in patients at high risk for Mg deficiency. Intracellular Mg deficiency may play a role in the pathogenesis of unexplained hypocalcemia in these patients, although one cannot yet definitely rule out other factors. Our findings suggest that in patients with normal serum creatinine concentrations who have persistent, unexplained hypocalcemia and who are at risk for Mg deficiency, a course of Mg therapy should be considered even if initial serum Mg concentrations are in the normal range. From 32 to 64 mEq of elemental Mg as a 50% solution of magnesium sulfate can be added to a patient's intravenous fluids each day as a continuous infusion for three to five days. Depending on the patient's oral Mg intake and ongoing medical problems and therapy, lower doses may be equally effective. Mg can also be administered by a controlled infusion pump in small amounts of dextrose and water in those patients who require fluid restriction, or it can be given intramuscularly in divided doses. In the presence of normal renal function, these doses of Mg rarely result in serum Mg concentrations of more than 2.5 mg per dl and are safe and inexpensive. Details of Mg treatment regimens are reviewed elsewhere.[1,32]

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Clinical Medicine

Plague Meningitis—A Retrospective Analysis of Cases Reported in the United States, 1970-1979

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Meningitis caused by Yersinia pestis *developed in 6 (6%) of a total of 105 patients with plague reported to the Centers for Disease Control from 1970 to 1979. Five of the six cases occurred in children aged 10 to 15 years. All six patients received antibiotic therapy before meningitis developed, which appeared between the 9th and 14th days after the onset of acute illness in five of the six patients. There were no neurologic sequelae. The antigenic and biochemical profiles of the* Y pestis *strains isolated from cerebrospinal fluid in the meningitis cases did not differ from those of the* Y pestis *strains obtained from blood and bubo aspirates in the other 99 patients, and neither did in vitro studies suggest antibiotic resistance. While plague meningitis is an uncommon complication of acute plague infection, physicians in the western United States should be aware that it may develop as much as 14 days after antibiotic therapy for the acute plague infection has been initiated.*

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While plague meningitis is an uncommon complication of human plague infections, its development is a possibility that treating physicians cannot afford to overlook. Of 105 cases of plague reported to the Centers for Disease Control (CDC) over a period of ten years—1970 to 1979—six of the patients had plague meningitis. We studied those 6 cases, comparing their case histories with those of the other 99 cases in which meningitis did not develop in an attempt to find any indication in the physical signs or symptoms or in the antibiotic therapy that might suggest a predisposition to the development of plague meningitis. We examined antimicrobial sensitivity of *Yersinia pestis* organisms, antigenic and biochemical characteristics of the organisms identified in cerebrospinal fluid (CSF) and the epidemiologic characteristics of all the 105 plague cases. We include in this report the case histories, physical findings and antibiotic therapy of the six cases in which plague meningitis did develop.

Patients and Methods

All human plague cases in this report were investigated by state and local health departments and the Indian Health Service in cooperation with the Plague Branch, Division of Vector-Borne Viral Diseases, Centers for Disease Control.

Case Definition and Study Population

We defined a case of plague as an illness reported to the CDC, occurring either in a person from whom *Y pestis* organisms were isolated or in one who showed a fourfold change in antibody titer (rise or fall) to *Y pestis*.

We defined a case of plague meningitis as an illness occurring in a patient from whom *Y pestis* was identified in the cerebrospinal fluid, or who had another form of documented plague infection, and a CSF Gram's stain showed either a bipolar, gram-negative rod or a positive fluorescent antibody test.

Laboratory Methods

We examined all bacteria by Wayson's stain and tested for growth characteristics in broth and agar, for mouse pathogenicity and for the production of F1 antigen in the fluorescent antibody test. We also tested all bacterial strains at 22°C and 37°C against a conditionally plague-specific phage in parallel with *Y pestis* strain 195/P and *Yersinia pseudotuberculosis* strain 1. The bacteria lysed by phage at both temperatures were considered *Y pestis*. We examined serologic specimens by the passive hemagglutination test for antibodies to *Y pestis*.[1] The Plague Branch laboratory confirmed all bacterial organisms and serologic tests.

We tested antimicrobial sensitivities of 4 CSF organisms, 2 bubo organisms from patients with meningitis and 94 other *Y pestis* organisms identified from patients without plague meningitis. For these sensitivity tests, we used microdilution minimal inhibitory concentration (MIC) test panels (Micro-Media Systems, Inc, Potomac, Md). The test panels included the following antibiotics: tetracycline, gentamicin, tobramycin, chloramphenicol, cephalothin, trimethoprim, amikacin, moxalactam, ampicillin, cefoxitin, cefamandole, rifampin, carbenicillin, penicillin, streptomycin, erythro-

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
CSF = cerebrospinal fluid
MBC = minimum bactericidal concentration
MIC = minimal inhibitory concentration

mycin, methicillin and sulfamethoxazole. The lowest concentration of antibiotic that resulted in no turbidity after 48 hours of incubation at 37°C was considered the MIC for a particular antibiotic. The minimum bactericidal concentration (MBC) was the minimal concentration of antibiotic that resulted in no growth of the organism when plated on trypticase soy agar and incubated at 37°C for 48 hours. We determined the MBC by plating onto trypticase soy agar plates with a calibrated loop (0.01 ml) the contents of the MIC dilution and the dilutions twofold and fourfold higher than the MIC dilution.

For biochemical characterization of strains of *Y pestis*, we used the API 20E System (Analytab Products, Plainview, NY). The dehydrated media contained in the microtubes were inoculated with suspensions of *Y pestis* (ten colonies, 48 hours old, suspended in 5 ml 0.85% sterile saline solution). We used the following in vitro tests for virulence markers of the *Y pestis* strains: the presence or absence of fraction I, V and W antigens; the presence or absence of the bacteriocin pesticin 2, and pigmentation on Congo red agar.[2]

For calculating relative risk estimates, we used standard Statistical Analysis System software packages.[3]

Results

Epidemiologic and Clinical Features

Of the 105 cases of plague infection reported to the CDC, plague meningitis developed in 6. Characteristics of patients in whom plague meningitis developed were similar to those of the other plague patients in respect to the sex ratio, geographic distribution and route of infection (Table 1), and the medical records did not indicate any early signs or symptoms in those patients in whom plague meningitis later developed compared with those patients whose clinical course did not include this complication. Five of the six cases were acquired in the summer months, and five occurred in children aged 10 to 15 years; the remaining case occurred in a 35-year-old woman.

TABLE 1.—*Characteristics of 105 Plague Patients, 1970-1979*

Patient Characteristics	*Patients With Plague Meningitis*	*Patients With Other Types of Plague*
Cases, No. (% of total)	6 (6)	99 (94)
Mean age (range), yr	17 (10-35)	24 (6 d-79)
Males, No. (%)	2 (33)	47 (47)
Females, No. (%)	4 (67)	52 (53)
Race, No. (%)		
Native American	1 (17)	27 (27)
White/other	5 (83)	72 (73)
Clinical features, No. (%)		
Buboes	3 (50)	81 (82)
Upper torso*	2 (33)	22 (22)
Lower torso†	1 (17)	59 (60)
None	3 (50)	18 (18)
Pneumonia	1 (17)	18 (18)
Osteomyelitis	1 (17)	0 (0)
Presumed mode of infection, No. (%)		
Flea bite	5 (83)	66 (67)
Direct tissue contact	1 (17)	18 (18)
Undetermined	0 (0)	15 (15)
State in which infection was acquired, No. (%)		
New Mexico	5 (83)	79 (80)
Arizona	1 (17)	16 (16)
All other	0 (0)	4 (4)

*Refers to cervical or axillary nodes
†Refers to femoral or inguinal nodes.

Clinical signs and symptoms of meningitis developed between the 9th and 14th days after the initial onset of illness in five of the six patients, and all five had received some form of antibiotic therapy before its development. The sixth patient's condition on presenting for treatment casts doubt on the number of days of illness reported (see case 1). Blood cultures were positive for *Y pestis* in three patients. One of the six patients had a pneumonic infiltrate suggestive of plague pneumonia. No neurologic sequelae were observed, though the death of one patient limited follow-up to five patients. None of the case histories of the patients with meningitis indicated prior head trauma, a neurosurgical procedure, an ear-nose-throat operation or lumbar punctures before the development of plague meningitis.

Upper torso (cervical or axillary) buboes were clinically apparent in two of the six meningitis cases (33%) and in 22 of the 99 patients without meningitis (22%). The relative risk of meningitis developing with the presence of cervical or axillary nodes was 1.7 (95% confidence interval, 0.3 to 8.6). Three of the meningitis cases (50%), and 18 (18%) of the plague patients in whom meningitis did not develop had septicemic plague; the relative risk of meningitis developing among septicemic cases was 4.0 (95% confidence interval, 0.9 to 18.4).

Strain Characteristics

The Centers for Disease Control received organisms isolated from CSF from four of the cases of plague meningitis. The CSF organisms showed antimicrobial susceptibility patterns similar to those from patients with nonmeningitic plague. MIC and MBC data were not different for meningitic and nonmeningitic strains within and between groups for each antibiotic tested. Antigenic profiles, API profiles, pigmentation and bacteriocin production were also identical in meningitic and nonmeningitic organisms. In one case (case 3), the bacterial strains isolated from the CSF were compared with those from the bubo aspirates; they were identical in all characteristics.

Reports of Cases

CASE 1. In June 1974, a 13-year-old Navajo girl from New Mexico presented as an outpatient at a local hospital with headache, dizziness, fever, vomiting and general malaise. She was given penicillin G benzathine intramuscularly and sent home with no diagnosis. Two days later she was admitted to hospital with complaints of abdominal pain, continued fever and headache. On physical examination she was lethargic and dehydrated, with insect bites on the lower extremities. A lumbar puncture was done. Two hours after admission, before all admission laboratory reports were available, the patient became hypotensive, had a cardiac arrest and died.

CSF and blood cultures were later found positive for *Y pestis*. An autopsy showed generalized petechiae, enlarged mesenteric nodes and hemorrhagic lymph nodes in the left femoral region. There was evidence of toxic myocarditis,

hemorrhagic pericardial effusion and edematous lungs. The spinal cord, meninges and brain were not studied at postmortem examination. Probable source of infection: plague-positive fleas from rodent harborage near the patient's home.

CASE 2. In February 1975, an 11-year-old boy from Albuquerque was admitted to hospital with a temperature of 38.3°C (101°F); a painful, firm, 10-cm mass in the right axilla; a laceration on the right forearm, and a partially evulsed fingernail on the right middle digit. A regimen of methicillin sodium and streptomycin was started for cellulitis and an axillary abscess. Blood and lymph node aspirate yielded positive cultures for *Y pestis*, and the patient's therapy was changed on the eighth day of illness to tetracycline. His condition improved and he was discharged to home, but was readmitted on the 11th day of illness with lethargy and a stiff neck. A lumbar puncture was done, and CSF cultures were found positive for *Y pestis*. The patient was treated with a course of chloramphenicol and recovered without sequelae.

Source of infection: a confirmed plague-positive dead coyote that the patient found and skinned three days before his illness.[4] Probable route of infection: direct inoculation of *Y pestis* from the coyote tissues via open lesions on the patient's right forearm and middle finger.

CASE 3. In July 1975, a 15-year-old boy from Pecos, New Mexico, had the sudden onset of fever, malaise and diaphoresis; he was seen by a physician who prescribed a course of tetracycline for an undiagnosed illness. Nine days after the onset of illness, a severe, bitemporal headache developed, and the patient was admitted to hospital with a presumptive diagnosis of *Hemophilus influenzae* meningitis. After four days of ampicillin therapy given intravenously, the patient was afebrile, felt well and was discharged to home on a regimen of tetracycline. *Y pestis* was subsequently grown from the CSF. Probable source of infection: flea bites by plague-infected fleas, probably from one of the family dogs.

CASE 4. In July 1978, a 10-year-old girl from Otero County, New Mexico, presented to a local emergency department with fever, chills, abdominal cramps, headache and neck pain. On physical examination no focus of infection was found. A course of oral penicillin was started and the patient was sent home with no diagnosis. She remained febrile, cervical lymphadenopathy developed and she had persistent neck pain. On the sixth day of illness she was admitted to hospital and treatment was changed to administration of cephalexin. A lumbar puncture was done and culture was positive for *Y pestis* on the ninth day of illness. The patient was given chloramphenicol intravenously and ampicillin, and her condition improved within two days, though a pulmonary infiltrate developed and she had clinical evidence of calcaneal osteomyelitis early in her hospital stay. Therapy was continued in the hospital for three weeks to ensure adequate treatment of the patient's osteomyelitis. On the 25th day after the initial onset of illness, the patient was discharged to home on a regimen of oral tetracycline. Recovery was uncomplicated, with no neurologic or pulmonary sequelae. Probable source of infection: a kitten that had become ill with ocular exudate and had been handled by the patient.

CASE 5. In August 1978, a 35-year-old woman from Bernalillo County, New Mexico, reported having had two days of chills, myalgias and fever. She saw a local physician who was unable to provide a specific diagnosis. The next day, culture of a blood specimen from the patient's 3-year-old daughter, who had been ill several days before the onset of her mother's illness, was positive for *Y pestis*. The patient was admitted to hospital and treated with a course of tetracycline for presumptive plague. After four days she was discharged to home receiving oral tetracycline.

Two days after completing a six-day course of tetracycline and 12 days after the initial onset of illness, fever and headache developed and the patient was readmitted with a diagnosis of presumptive plague meningitis. A Gram's stain of the CSF showed gram-negative, bipolar-staining rods. The patient was given chloramphenicol intravenously and recovered without sequelae. Probable source of infection for both this patient and her daughter: infected fleas brought to the home by pet dogs.

CASE 6. In May 1979, a 13-year-old girl from Yavapai County, Arizona, was admitted to hospital with left lower quadrant tenderness and a subcutaneous abscess of the upper left anterior thigh. The initial clinical impression was pelvic inflammatory disease and an abscess of the left anterior thigh. After ten days of a regimen of penicillin given intravenously, erythromycin and cephalosporins, a severe headache and stiff neck developed, and she had a temperature of 38.9°C (102°F). On the 14th day of illness, a CSF culture grew both *Salmonella* species and *Y pestis*. The patient was then treated with a regimen of intravenous ampicillin and chloramphenicol; she made a gradual recovery and was discharged to home with no neurologic deficits. Probable source of infection: Investigation revealed rodent plague activity within 0.4 km (1/4 mi) of the patient's home. Infected fleas were probably brought into the patient's home by the family dogs.

Discussion

Y pestis infection most commonly occurs as the bubonic form of plague, which is simply an acute, usually regional, lymphadenitis. Prior reports have indicated that when plague meningitis occurs, it usually follows the bubonic infection.[5-7] The incidence of plague meningitis is low, ranging from 0.2% to 7.0% in published reports on plague infections in humans.[5,8,9]

The pathophysiology of plague meningitis is not well understood. Butler and co-workers have suggested that axillary or cervical buboes may predispose to meningitis through more direct lymphatic connections to the meninges.[9] Our data also suggest an increased risk of the development of meningitis in patients with cervical or axillary buboes, though the association was not statistically significant. In addition, septicemic plague also may be a risk factor for the development of meningitis: this increased risk is probably a result of bacteremia that leads to colonization of the meninges with *Y pestis* (although in a recent study on septicemic plague, no septicemic plague occurred in patients with meningitis[10]). Others have suggested that the meninges may be more susceptible to infection from organisms already adapted to mammalian host systems, such as in direct blood transmission from infected hosts.[11] Our data, however, do not support this suggestion: 19 of the cases of plague infection resulted from direct contact with infected animal tissues, and in only one did meningitis subsequently develop (case 2).

The most likely explanation for the development of plague

meningitis, consistent with observations of other researchers,[12] is that ineffective antibiotic therapy for the acute stages of plague infection allows the development of meningitis later in the course of the illness. The combination of the type of drug used, the rapidity with which it is administered following the onset of illness and the length of time it is administered may well be the important factors in successful treatment.

The findings of this study tend to support this theory. In case 2, the patient received the recommended antibiotics for plague infection—streptomycin and tetracycline—as well as methicillin, before the development of meningitis. The streptomycin and methicillin were not administered until the third day after the onset of illness, however, and the tetracycline was not administered until the eighth day. This may have been too late to prevent the spread of infection to the meninges. The patient in case 3 received a course of tetracycline, a recommended antibiotic for plague therapy, on the second day of acute illness. The dosage of 250 mg every six hours, however, was probably inadequate for a 15-year-old boy weighing 75 kg (165 lb). It is also possible that the patient did not comply with his treatment regimen, as he was not initially admitted to hospital. Case 5 is similar to case 3 in the ineffectiveness of tetracycline to prevent the development of meningitis. A course of tetracycline was started on the second day of illness, when the patient's daughter was diagnosed as suffering from plague infection. The tetracycline was taken for a total of eight days, four of them supervised in hospital. While poor compliance with the prescribed regimen does not seem to be a factor in this case and appropriate therapy was begun early in the acute illness, it is possible that the duration of the treatment period with tetracycline was inadequate. Cases 1, 4 and 6 are more consistent with cases of plague meningitis that have been described in the literature in that the antibiotics used before the development of meningitis were not the antibiotics of choice for treating plague.

Although tetracycline or doxycycline was included in the treatment regimen of four of the meningitis cases in this study—cases 2, 3, 5 and 6—we cannot conclude that tetracycline therapy predisposes to meningitis, as numerous other patients were effectively treated with it alone or in combination with other antibiotics. Tetracycline, however, does not readily cross the blood-brain barrier, and it is possible that the level of antibiotic in the central nervous system is insufficient to inhibit infection. If the meninges are seeded in the early stages of acute infection, as has been suggested,[6,7] tetracycline would have little effect. For the same reason, streptomycin therapy would also be ineffective (case 2).

Our study of the meningitis and nonmeningitis plague cases did not disclose any indicators to warn of the impending development of meningitis. Such clinical signs as the degree of temperature elevation were similar in both groups, and antigenic and antibiotic profiles of *Y pestis* strains were identical in the meningitic and nonmeningitic strains. Our investigation is obviously limited by the small number of plague meningitis cases. As additional cases are diagnosed, further analyses may reveal clinical or laboratory correlates for the development of the meningitis as an acute plague complication. Unfortunately, many questions concerning the pathophysiology of plague meningitis will remain unanswered until more clinical data are collected or until a suitable animal model is developed to study it. Nevertheless, despite limited understanding of the development of this complication, greater clinician awareness of meningitis as a sequela to acute plague infection could prevent its occurrence.

The choice of an antibiotic known to be effective against *Y pestis* and its administration for an adequate period of time are critical in the treatment of plague infection. If meningitis develops, 50 mg per kg per day of intravenous chloramphenicol, given in four doses a day for ten days, provides adequate therapy. Clinicians should also schedule follow-up examinations soon after discharging plague patients from the hospital. Educating the patients to the risks of the development of meningitis would also be a wise precaution, encouraging them to follow their treatment regimen carefully and to report any early central nervous system signs or symptoms.

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Group B Streptococcal Soft Tissue Infections Beyond the Neonatal Period

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In one year sporadic soft tissue infections due to group B streptococci were identified in 37 patients beyond the neonatal period. Serious underlying conditions were present in 25 patients (68%), including 17 (46%) who had diabetes mellitus and 4 (11%) with paraplegia. Unlike previous reports, 12 patients (32%) were previously healthy. Infection developed in 8 persons as a result of minor trauma. The mean age of the normal hosts was 20.9 years, whereas the mean age of patients with underlying disease was 44.2 years (P<.0005). The clinical spectrum was varied and included abscess formation in 17 patients (46%). All patients required treatment with antibiotics and 28 (76%) required admission to hospital. Complete recovery occurred in 33 patients (89%) while 4 with diabetes required amputation of infected extremities. Group B Streptococcus *was the only organism identified in 22 patients (59%) while mixed organisms were cultured in 15 (41%), including* Staphylococcus aureus *in 12 and gram-negative enteropathogens in 4. Group B streptococcal soft tissue infections beyond the neonatal period are common and may even involve normal hosts.*

(McCarty JM, Haber J: Group B streptococcal soft tissue infections beyond the neonatal period. West J Med Nov; 147:558-560)

Lancefield group B streptococci *(Streptococcus agalactiae)* are recognized as common pathogens in neonates.[1] Infections in older patients have been described less frequently and usually occur in postpartum women, persons with diabetes mellitus and immunocompromised hosts.[2-5] Infections are considered unusual in normal adults, and involvement of the skin and underlying soft tissues is seen infrequently.[6] In recent years we have noted in our hospital microbiology laboratory frequent group B streptococcal organisms identified in wounds. In 12 months 37 patients proved to have soft tissue infections due to group B streptococci, and we noted that many of these patients were otherwise normal.

Patients and Methods

Medical records of all patients older than 2 months of age with group B streptococcal organisms identified from the skin and adjacent soft tissues at Valley Medical Center, Fresno, California, between April 1, 1984, and April 1, 1985, were reviewed. The study period was arbitrarily chosen and the results are consistent with our continued observations. Group B streptococci were identified by colony morphology, CAMP testing, bacitracin sensitivity and agglutination with group-specific antiserum.

Results

In the one-year study period, group B streptococcal organisms were recovered from wound cultures of 37 non-neonatal patients (Table 1). In all patients the physical findings were consistent with cellulitis—erythema, swelling and tenderness. In all, 14 patients were febrile and 17 had abscess formation requiring incision and drainage of purulent material. Preexisting medical conditions were seen in 25 patients. Of these, 17 had diabetes mellitus: 11 with infected extremities, 3 with abscesses in the inguinal region, 2 with buttock abscesses and 1 with cellulitis of the labia majora. Other patients with underlying medical problems included four paraplegic patients with infected sacral decubitus ulcers, an intravenous drug abuser with a hand abscess, a patient with chronic renal failure with cellulitis around an arteriovenous fistula, a person with chronic alcoholism with cellulitis over the sternoclavicular joint and a postpartum patient with an infected cesarean section wound. Five of the diabetic patients with infected extremities and two of the paraplegic patients had prior episodes of soft tissue infections, although group B streptococci were previously identified in only three diabetic patients. No infections were nosocomial.

Twelve patients had no history of preexisting medical conditions, and most had infected extremities due to trauma. In one 14-month-old infant group B streptococcal organisms were identified from an impetiginous skin lesion, and one 44-year-old man was admitted to hospital with an infected sunburn.

Surgical therapy was required in 24 patients, including incision and drainage of abscesses in 17, debridement of devitalized tissue in 3, removal of an arteriovenous fistula in 1 and amputation of nonviable extremities in 4 diabetic patients. All patients received antimicrobial therapy while 28 required hospital care. A total of 36 patients was seen in follow-up and all eventually recovered.

The patients ranged in age from 14 months to 65 years. The previously healthy patients were significantly younger (mean age 20.9 years versus 44.2 years) than those with underlying medical problems ($P < .0005$, unpaired t test). In

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all, 30 patients were male and 7 were female. The duration of symptoms ranged from two days to two years. Fourteen patients had a history of fever, chills or both.

Group B *Streptococcus* was the only organism identified in wounds in 22 patients, including 11 of 17 patients with diabetes mellitus, 4 of 8 previously healthy patients with trauma and 2 of 4 with paraplegia. Mixed organisms were cultured in 15 patients: organisms included *Staphylococcus aureus* in 12 and gram-negative enteric pathogens in 4. Group B *Streptococcus* was the only organism identified in 12 of 17 patients with abscesses, although anaerobic cultures were infrequently done. Gram's stains of infected material were available in 26 patients. In 22 specimens with organisms seen, 18 showed a predominance of streptococci. Blood cultures were done in only seven patients, including five patients with fever. All were negative, although one patient was re-

TABLE 1.—*Clinical Characteristics of Patients With Group B* Streptococcus *Soft Tissue Infections*

Case #	Age, yr	Sex	Duration of Complaints	Fever	Chills	Site and Type of Infection	Underlying Problem	Other Organisms Isolated	Blood Culture	Therapy	Outcome
1	49	♀	3 wk	No	No	Inguinal abscess	DM	...	ND	I&D; Dicloxacillin PO	Resolved
2	52	♂	6 d	No	No	BKA stump abscess	DM	*Staphylococcus aureus*	ND	Debridement; nafcillin IV	Resolved
3	56	♂	6 mo	No	No	Infected toe ulcer	DM	*Staphylococcus aureus*	ND	Nafcillin IV; amputation	Resolved
4	35	♂	3 wk	No	No	Inguinal abscess	DM	Gram-negative enteropathogen		Pencillin, gentamicin sulfate	Resolved
5	50	♀	4 d	No	No	Cellulitis of labia majora	DM	..	ND	Erythromycin PO	Resolved
6	54	♂	1 mo	No	No	Infected toe ulcer	DM	..	ND	Cefazolin IV; amputation	Resolved
7	55	♂	4 d	No	No	Hand abscess	DM	..	ND	I&D; cefazolin IV	Resolved
8	19	♀	20 d	No	No	Cellulitis of cesarean section wound	Post-partum	*Staphyloccus aureus*	ND	Ampicillin IV	Resolved
9	60	♂	5 d	No	No	Cellulitis of hand	DM	...	ND	Dicloxacillin PO	Resolved
10	65	♂	1 d	Yes	Yes	Infected toe ulcer	DM	...		Ampicillin IV, gentamicin	Eventual amputation
11	62	♀	4 d	No	No	Hand abscess	DM	*Staphylococcus aureus, Klebsiella oxytoca, Citrobacter freundii*	.	I&D; cefazolin IV	Resolved
12	56	♀	2 d	Yes	No	Toe abscess	DM	*Escherichia coli*		I&D; nafcillin IV	Resolved
13	40	♂	2 wk	Yes	Yes	Chest wall abscess	Ethanol abuse	...	.	I&D; penicillin IV	Resolved
14	59	♂	3 d	No	No	Finger abscess	DM	.	ND	I&D; cefazolin IV	Resolved
15	50	♂	3 d	Yes	No	Buttock abscess	DM	..	ND	I&D; ampicillin PO	Resolved
16	31	♂	1 wk	Yes	No	Infected decubitus ulcer	Para-plegia	*Staphylococcus aureus*	ND	Debridement; erythromycin PO	Eventual skin graft
17	65	♀	?	?	?	Foot abscess	DM	...	ND	I&D; cefazolin IV	Eventual osteomyelitis and amputation
18	29	♂	4 d	Yes	Yes	Infected decubitus ulcer	Para-plegia	.	ND	Dicloxacillin PO	Eventual skin graft
19	21	♂	3 d	No	No	Inguinal abscess	DM	...	ND	I&D; cefazolin IV	Resolved
20	28	♂	6 d	No	No	Infected decubitus ulcer	Para-plegia	..	ND	?	?
21	39	♀	3 d	No	No	Perirectal abscess	DM	.	ND	I&D; cefazolin IV, clindamycin, gentamicin	Resolved
22	24	♂	2 d	Yes	Yes	Infected decubitus ulcer	Para-plegia	*Staphylococcus aureus*	.	Debridement; clindamycin IV, gentamicin	Resolved
23	34	♀	?	No	No	Infected arterio-venous shunt	Chronic renal failure	*Klebsiella oxytoca*	ND	Cefazolin IV; graft removal	Resolved
24	39	♂	2 d	Yes	Yes	Hand abscess	IV drug abuse	*Staphylococcus aureus*	ND	I&D; cefazolin IV	Resolved
25	61	♂	?	No	No	Infected leg ulcer	DM	*Staphylococcus aureus*	ND	Dicloxacillin PO	Resolved
26	10	♂	6 d	No	No	Cellulitis of leg	Trauma	...	ND	Oxacillin IV	Resolved
27	50	♂	2 wk	No	No	Cellulitis of foot	Trauma	...	ND	Dicloxacillin IV	Resolved
28	9	♂	2 d	No	No	Hand abscess	Trauma	...	ND	I&D; cefazolin IV	Resolved
29	19	♂	1 d	No	No	Hand abscess	Human bite	..	ND	I&D; nafcillin IV, clindamycin, gentamicin	Resolved
30	15	♂	3 d	Yes	No	Cellulitis of hand	Trauma	*Staphylococcus aureus*	ND	Cefazolin IV	Resolved
31	30	♂	1 wk	Yes	No	Axillary abscess	...	*Staphylococcus aureus*	ND	I&D; cefazolin IV	Resolved
32	2	♂	4 d	Yes	No	Facial cellulitis	Trauma	*Staphylococcus aureus*	.	Nafcillin IV	Resolved
33	1	♂	3 d	Yes	No	Impetigo	..	*Staphylococcus aureus*	ND	Dicloxacillin PO	Resolved
34	44	♂	3 d	No	No	Cellulitis of leg	Sun-burn	.	ND	Erythromycin IV	Resolved
35	18	♂	2 d	Yes	Yes	Cellulitis of hand	Trauma	...	ND	Cefazolin IV	Resolved
36	24	♂	2 yr	No	No	Buttock abscess	..	...	ND	I&D; oxacillin IV	Resolved
37	29	♂	5 d	Yes	No	Neck abscess	...	..	ND	I&D; cefazolin IV	Resolved

BKA=below-the-knee amputation, DM=diabetes mellitus, I&D=incision and drainage, IV=intravenously, ND=not done, PO=by mouth, ?=data not available

ceiving oral antibiotics when blood specimens were drawn for culture.

Discussion

Group B streptococci usually cause infections in neonates. In adults the most frequent types of disease include genital tract infections in postpartum women and bacteremia, meningitis, pneumonia, septic arthritis and pyelonephritis.[2,7] The organism is usually recognized as an opportunistic pathogen in patients with underlying medical conditions.[2,3,7-9] Soft tissue infections have not been well described and frequently involve patients with surgical wounds or with diabetes mellitus and peripheral vascular disease.[3,8,10] There have also been occasional reports of paronychia, impetigo, penile cellulitis and infection of burn wounds and decubitus ulcers associated with group B streptococci.[6,9,11-14]

Our data suggest that group B streptococcal soft tissue infections may be more common than previously recognized. These findings are also notable in that 32% of our patients were previously healthy and abscesses developed in 46%. Patients without underlying medical problems were usually younger and most had infections at sites of minor trauma. Our high ratio of male to female patients (4.3:1) corresponds with that of other series.[7,15]

Previous reports of group B streptococcal soft tissue infections frequently note the presence of other microorganisms on culture and, thus, question the role of group B *Streptococcus* as a primary pathogen.[3,8] The presence of group B *Streptococcus* as the sole organism identified in wounds in 59% of our patients indicates that it can function as a primary pathogen. Although in patients with mixed infections pathogenicity cannot be proved, streptococci were the predominant organisms on 18 of 22 wound Gram's stains with organisms seen. Also remarkable was its presence as the only organism in 71% of patients with abscesses. The presence of *Staphylococcus aureus* as a copathogen in 12 patients is notable because this has been seen in studies of pneumonia and bacteremia caused by group B *Streptococcus*.[16,17]

Bacteremia was documented in none of our patients although blood cultures were done in only seven. The prevalence of bacteremia in this group of patients is not known as group B streptococcal bacteremia may be brief and not accompanied by hypotension.[2,16] No bacteremias due to group B *Streptococcus* were identified in non-neonates at our institution during the study period. Although some authors have found the skin to be a common source of group B streptococcal bacteremia in adults, most have shown that soft tissue infections infrequently lead to bloodstream invasion.[2,8,16,18,19]

Despite the presence of group B *Streptococcus* as the sole wound isolate in 22 of our patients, antistaphylococcal antibiotics were used in most patients. It is unclear why these were chosen, but the cost of therapy could have been decreased with more specific therapy. Penicillin is the antibiotic of choice for group B streptococcal infections.

Group B streptococcal soft tissue infections usually occur in unhealthy hosts. They are frequently seen in otherwise healthy persons, however, and these patients are younger. Infected patients are more frequently male than female. Group B *Streptococcus* frequently leads to abscess formation and is usually the only organism involved.

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Treatment of the Obstructive Sleep Apnea Syndrome

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The obstructive sleep apnea syndrome is a disorder of sleep and breathing that is being recognized with increasing frequency. The pathophysiologic consequences range from mild sleepiness to life-threatening cardiovascular and respiratory decompensation. The primary forms of treatment are directed at modifying the upper airway with either an operation or continuous positive airway pressure. Aside from tracheostomy, which is virtually always successful, other forms of treatment have met with varying results. Ancillary therapy, including oxygen, weight loss and drugs, is often helpful but seldom curative. Follow-up sleep studies are necessary to evaluate the effectiveness of treatment. Selecting therapy for a patient with obstructive sleep apnea requires a comprehensive evaluation including polysomnography, special examinations of the upper airway and assessing the cardiopulmonary status. Therapy is based on the severity of disease and must be tailored to each patient.

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Since its first description two decades ago, the obstructive sleep apnea syndrome has become the subject of extensive investigation and clinical activity. With progress in understanding the pathophysiology, various surgical and nonsurgical treatments have been developed and are available to clinicians treating sleep apnea. Most reviews of this subject have focused on the pathophysiology, but several reviews of treatment have appeared recently.[1-4] In this article we focus on treatment and particularly on clinical reports that permit a critical appraisal of the efficacy of varied treatments. The review will focus on the condition as it occurs in adults because most of the literature deals with this age group.

In view of the newness of the current concepts of sleep apnea, it is not surprising that the indications and efficacy of various treatments remain controversial. The very number of available choices testifies to the lack of a universally acceptable solution. Most treatments are effective only to varying degrees in selected groups of patients. Furthermore, most therapies represent a significant intervention in terms of patient involvement, risk of complication or cost. Thus, selecting the best therapy for each patient requires an analysis of risk versus benefit. Unfortunately, relatively few systematic or controlled studies have been conducted that provide the necessary information for this analysis. The emphasis of this review will be on information that facilitates this risk-benefit analysis.

Clinical Manifestations

The clinical manifestations of obstructive sleep apnea are related to upper airway obstruction, sleep disruption and the respiratory and cardiovascular consequences of disordered breathing.[5,6] Snoring is universally present when both patients and families are carefully interviewed. Less frequent indications of obstruction include struggling for breath and choking, with repeated arousals. The consequences of sleep disruption are similar to those of sleep deprivation, with pathologic sleepiness as the primary symptom. Other symptoms include fatigue, personality change, depression, impotence and automatic behavior. The respiratory consequences are related to the extent of hypoxemia and hypercapnia that develop with the hypoventilatory episodes as well as to their frequency. Thus, more advanced cases are associated with pulmonary hypertension, cor pulmonale, chronic carbon dioxide retention and polycythemia. Most patients, however, do not manifest these disturbances, presumably because their ventilation during wakefulness is normal enough to prevent these complications of chronic hypoxia. The cardiovascular consequences are systemic hypertension and cardiac arrhythmias during sleep. Sudden death has occurred in patients with sleep apnea.[6]

Pathophysiology

The pathophysiology of the obstructive sleep apnea syndrome has been reviewed recently and will not be considered in detail.[7-9] For orientation, however, a brief summary is necessary.

The sleep apnea syndrome is a group of clinical conditions characterized by abnormal breathing in sleep and sleep fragmentation. In patients with the obstructive sleep apnea syndrome, obstruction of the upper airway during sleep results in intermittent hypoventilation or overt apneas. The resulting hypoxemia and hypercapnia produce arousal with restoration of the airway and the resumption of breathing. When this sequence of events occurs often enough—typically hundreds of times each night—the combined effects on sleep and cardiopulmonary function produce the morbidity associated with this condition. In a small number of patients, those with predominantly central apneas, an absent respiratory effort rather than obstruction appears to be the principal cause of apneas. Recent investigation suggests, however, that many of these patients also have associated upper airway dysfunction and benefit from measures that improve airway patency.[10,11]

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
REM = rapid eye movement
SI = severity index

The causes of upper airway obstruction in the obstructive sleep apnea syndrome are complex and controversial. The site of the obstruction has been identified as the oropharynx and nasopharynx.[12-14] Gross anatomic factors play a major role in cases associated with tonsillar hypertrophy, macroglossia and micrognathia.[15-17] Even in patients without an obvious pathologic disorder of the upper airway, measurements by computed tomography identify substantial narrowing of the oropharyngeal airway compared with normal persons.[18] Functional abnormalities have been identified, including increased upper airway resistance and increased compliance of the upper airway.[19,20] Reductions in respiratory drive have been identified by altered breath timing and by decreased diaphragmatic and upper airway muscle activity, and although their cause is uncertain, they may be significant elements in the pathogenesis of obstruction and apneas.[21-23]

Thus, a variety of mechanisms contribute to the upper airway obstruction in this disorder, but identifying the principal cause in an individual patient is difficult. When surgical treatment is contemplated, the anatomy of the upper airway and the precise site of obstruction become a major consideration. Of the many investigational techniques used to assess the upper airway, nasopharyngeal endoscopy, lateral cephalometrograms and computed tomography appear to be clinically practical and may have some value for guiding surgical decisions.[12,14,24-27] Physical examination occasionally reveals gross abnormalities of the facial skeleton or oropharynx, but in most patients the results of an examination are not a reliable guide to therapy or a predictor of outcome.[28,29]

Treatment

The treatment of sleep apnea has focused on correcting the various physiologic derangements just discussed. For the purpose of this review, treatment will be classified according to therapies directed at airway patency, including surgical procedures of the upper airway, prosthetic devices and continuous positive airway pressure (CPAP), and ancillary therapies directed at disturbances of gas exchange and abnormalities of respiratory rhythm (Table 1).

Surgery of the Upper Airway

Surgical treatment of obstructive sleep apnea appeals to patients and physicians alike as a permanent "fix" for a complicated and troubling disorder. As the pathophysiology of the obstructive sleep apnea syndrome has become defined, various surgical treatments have been developed. The relative efficacy of individual procedures is somewhat difficult to assess from the literature. Central to this problem is the broad spectrum of severity of this disease and the lack of a clear definition of what constitutes a "cure." An operation is a powerful placebo, and thus subjective improvement alone cannot be accepted as proof of efficacy. Such a conclusion must be supported by objective data, including, at a minimum, a complete postoperative polysomnogram.

Tracheostomy. Tracheostomy was the first efficacious procedure described for sleep apnea and remains the procedure against which all others should be measured.[30,31] Guilleminault and co-workers reported a series of 50 patients with severe obstructive sleep apnea who underwent tracheostomy.[32] Before the procedure, all but one patient had an oxygen desaturation to 30% or lower and all had an apnea index of 65 or more apneas per hour. Following the operation, the apnea index dropped to 5 or less and the lowest desaturation was 82%. Of these patients, 47 were employed or in school within three months postoperatively. Weitzman and colleagues showed more consolidated sleep with fewer arousals in ten sleep apnea patients following tracheostomy.[33] Obstructive and mixed apneas were eliminated. Complications of tracheostomy, however, though not severe, are frequent. Guilleminault and associates reported that 42% of their patients experienced recurrent low-grade infections and airway granulations.[32] Conway and co-workers noted similar problems, including stomal stenosis, in 8 of 11 patients.[34] Such difficulties may be lessened with the skin-flap tracheostomy as described by Fee and Ward.[35]

TABLE 1.—*Treatment of Obstructive Sleep Apnea*

Modification of the upper airway
Tracheostomy
Uvulopalatopharyngoplasty
Nasal operation
Orthognathic operation
Nasal CPAP
Prosthetic devices
Adjunctive therapy
Weight reduction
Oxygen
Pharmacotherapy
Position

CPAP = continuous positive airway pressure

Clearly, tracheostomy cures sleep apnea. Just as obvious, however, are the medical and social problems associated with a permanent tracheostomy, and these have stimulated the search for alternative therapies.

Uvulopalatopharyngoplasty. Other surgical procedures for the obstructive sleep apnea syndrome involve enlarging or expanding the upper airway, thereby preventing its collapse. The selection of one or more of these procedures should be based on objective findings documenting the level or levels at which the obstruction occurs. A simple procedure, such as adenotonsillectomy, may be all that is necessary in selected patients. Eliaschar and colleagues showed a significant reduction in the number of obstructive apneas in children undergoing tonsillectomy for obstructive sleep apnea.[36] Orr and Martin showed that tonsillectomy in adults with even relatively mild tonsillar enlargement alleviates sleep apnea.[15]

Uvulopalatopharyngoplasty is probably at present the most frequently done procedure for sleep apnea. Initially described in the American literature by Fujita and associates, this procedure involves shortening the soft palate, amputating the uvula and removing redundant lateral and posterior pharyngeal wall mucosa from the oropharynx.[37] Of their initial 12 patients, 11 described a subjective abatement of daytime sleepiness. Sleep indices, including the number of apneas, oxygen saturation and the number of arousals, were significantly improved for the group as a whole. Three patients, however, were essentially unchanged, one patient was worse and three others had improvement but continued to show evidence of residual sleep disturbance when evaluated by poly-

somnography. Thus, severe sleep apnea may be converted to a milder disease. Simmons and co-workers reported that 17 of 20 patients who underwent uvulopalatopharyngoplasty reported symptomatic improvement.[28] Objective improvement in sleep indicators, including the apnea index and oxygen saturation, was exhibited by only 50% of this group. Katsantonis and associates evaluated their results by measuring the "severity index (SI)"—that is, the number of obstructive events per hour resulting in oxygen desaturation below 85%.[29] Nearly two thirds of their series of 31 patients showed a reduction in the "SI" of better than 50%. While all authors report a substantial reduction in snoring as well as symptomatic improvement, there is no clear agreement on what constitutes a cure of sleep apnea or, for that matter, what is meant by significant improvement. Using rigorous guidelines for decannulation, Borowiecki and Sassin were unable to decannulate ten of ten patients who underwent uvulopalatopharyngoplasty in conjunction with tracheostomy.[38] The likelihood of a successful result may improve with careful patient selection based on special preoperative studies.

Using the Mueller maneuver, Sher and colleagues evaluated patients who had fiber-optic nasopharyngoscopy to determine the anatomic site of airway collapse.[24] Patients showing collapse at the soft palate received uvulopalatopharyngoplasty, and 87% had significant improvement. Walsh and Katsantonis evaluated 16 patients with somnofluoroscopy before and after uvulopalatopharyngoplasty.[39] Those patients whose airways were narrowest in the mid and upper oropharynx tended to respond more favorably.

Nasal surgery. Nasal operations have been shown to diminish sleep apnea in selected patients.[40-42] In general, these are patients with obvious obstruction due to deformity of the nasal septum, or polyps, and relatively mild sleep apnea. Patients with moderate to severe sleep apnea are not as likely to benefit from a nasal operation alone, though it may be a useful adjunctive procedure. Nasal obstruction has been related to excessive daytime sleepiness and arousals, periodic breathing and hypopneas during sleep.[43] Following a nasal procedure, 12 of 14 patients had improvement, evidenced by more consolidated sleep and fewer arousals.

Orthognathic surgery. Mandibular deficiency has been associated with sleep apnea. Bear and Priest reported the case of one patient with obvious mandibular retrognathism and sleep apnea who was cured by surgical advancement of the mandible.[44] More recently, using lateral cephalometric skull radiographs, Guilleminault and co-workers have shown subtle facial skeletal abnormalities in patients with sleep apnea.[25] In their series, patients had a narrow posterior airway space and a low-lying hyoid bone. Accordingly, they have devised a procedure that advances the anterior-inferior mandibular arch, together with the genioglossus muscle, and suspends the hyoid bone. In their series of five patients in which uvulopalatopharyngoplasty failed for three, four of five showed significant subjective and objective improvement.[45] Carrying this concept a step further, the authors did maxillary, mandibular and hyoid advancements in a series of nine patients.[46] Most of these patients showed some mandibular deficiency radiographically, but two had normal facial skeletal relationships. All patients showed significant symptomatic improvement and pronounced improvement on postoperative polysomnography.

Miscellaneous surgical procedures. The problem of hypopharyngeal collapse has been addressed by Patton and Thawley using a procedure that involves sectioning the hyoid bone and expanding it using a stainless-steel brace.[47] Their work in dogs has shown that the hypopharynx is enlarged and is less likely to collapse with this procedure, but the experience in patients is too limited to assess at this time. Fujita and associates have recently presented another approach to the problem of hypopharyngeal collapse.[48] Tongue reduction by midline laser glossectomy was done in selected patients with good results. This procedure, too, requires further study.

Surgical treatment has also been used to reduce weight in morbidly obese patients as the principal therapy for the obstructive sleep apnea syndrome.[49,50] Weight loss as therapy will be discussed in a subsequent section.

Prosthetic Devices

The use of prosthetic devices in the treatment of the obstructive sleep apnea syndrome is based on the same principles used in surgical treatment. The two areas of focus anatomically are the nasopharyngeal inlet and the posterior tongue. Collapse at the level of the soft palate has been managed with a rubber nasopharyngeal airway, commonly used for postanesthetic airway management.[51,52] The mandible may be temporarily advanced by inserting an acrylic dental appliance before sleep.[53,54] Cartwright and Samuelson have used a tongue-retaining device to hold the tongue in a more anterior position during sleep.[55] This device has also been used successfully in some patients who have not had improvement following uvulopalatopharyngoplasty.[56] Nasal breathing is obligatory with both the dental appliance and the tongue-retaining device, and thus the nasal airway must be adequate for them to be of benefit. The disadvantage of prosthetic devices is the need to insert them nightly and the discomfort associated with wearing them. Experience with all of these devices is limited, but they may prove to be useful in selected patients.

Nasal CPAP

Successful treatment of sleep apnea by using continuous positive airway pressure (CPAP) was first reported by Sullivan and colleagues in 1981.[57] Subsequent reports have shown this therapy to be almost uniformly successful in a broad spectrum of patients with the obstructive sleep apnea syndrome.[58-62] Nasal CPAP appears to work as a "pneumatic splint" of the upper airway, the positive pressure preventing passive collapse of soft tissues during inspiration. Apneas and hypopneas are eliminated, and consolidated sleep returns. Periodic oxygen desaturation is corrected, though hypoxemia may persist in patients having alveolar hypoventilation or chronic lung disease, and such patients may require oxygen supplementation. Symptomatic improvement is dramatic, with pathologic daytime sleepiness reduced or eliminated, a result recently confirmed by multiple sleep latency tests.[63]

Despite the elegant simplicity of the concept, CPAP has not been easy to implement, and patient compliance has been a problem. Applying pressure through the nose appears to be the most suitable for patient comfort and ease of application. Sullivan and colleagues initially used intranasal tubes, and other investigators have used a similar design.[57,60,62] Most investigators, however, use a mask held against the face with sufficient pressure to prevent air leak. Commercial versions of this technique are now available. Initially recommended for the short-term relief of sleep apnea, nasal CPAP has been used for long-term care. Not all patients accept this therapy,

however. In a series of 50 patients treated by Sullivan and co-workers, 35 selected nasal CPAP for long-term use.[59] Recent reports from this country indicate that patient acceptance may be as low as 60%.[64,65] The reasons for dissatisfaction include irritation of skin and eyes, the latter from air leaks around the mask, nasal congestion and sore throat and the inability to tolerate the noise. Thus, implementing nasal CPAP, particularly for long-term use, requires careful patient selection, training and follow-up.

Ancillary Therapies

Weight reduction. Weight loss should be emphasized in the treatment of sleep apnea. Burwell's classic description of the pickwickian syndrome documents the beneficial effect of relatively modest weight loss on sleepiness and on cardiopulmonary function.[66] Early reports of case series of sleep apnea refer to the benefits of weight loss but without systematic observations.[5] More recently a well-controlled study of 16 patients showed fewer apneas and reduced oxygen desaturation along with lessened daytime sleepiness in patients who lost about 20 kg (45 lb) when compared with a similar group of patients who did not lose weight.[67] Several studies in patients with morbid obesity have shown improved oxygen saturation and usually reduced apnea frequency after weight loss produced by a weight-reducing operation.[49,50,68] Thus weight loss can be beneficial in patients with the obstructive sleep apnea syndrome and obesity of a moderate to a severe degree. Subjective improvement usually accompanies these objective changes, but some disturbance of sleep and breathing usually remains.

Oxygen therapy. The role of oxygen in the treatment of sleep apnea has been surprisingly controversial. The argument against oxygen therapy is based on the belief that supplemental oxygen will delay arousal from apnea. Motta and Guilleminault presented this argument based on limited observations in three patients with obstructive apneas and one with central apneas in whom oxygen administration approximately doubled the duration of apneas during non-rapid-eye-movement (REM) sleep and respiratory acidosis was made worse.[69] Martin and associates subsequently reported the cases of eight patients with obstructive apnea in whom oxygen administration consistently reduced the severity of oxygen desaturation.[70] In five patients, long-term oxygen therapy substantially reduced the number of apneas. Smith and co-workers reported the cases of 15 patients who improved or did not worsen with oxygen when apnea frequency, duration and degree of desaturation were examined.[71] The same investigators subsequently reported that long-term—that is, one-month—oxygen therapy did not correct pathologic sleepiness despite improvement of nocturnal oxygenation.[72]

The combined experience of these reports suggests that in most patients with obstructive apnea, oxygen can be used safely and will produce beneficial effects on respiration. In some patients, perhaps those with high-grade upper airway obstruction, apnea duration may be prolonged. The concern that such prolongation may produce a worse outcome is not supported by published data. It should be noted, however, that the effect of oxygen use has been studied carefully in only a small number of patients, with considerable individual variation in each investigation. We believe that the dangers of profound hypoxemia are greater than the theoretic concerns about prolonged apnea and that oxygen therapy should not be withheld when hypoxemia is profound, particularly when secondary effects such as bradyeardia, pulmonary hypertension or erythrocytosis are present. The effect, however, of oxygen therapy on a patient with high-grade airway obstruction or chronic respiratory acidosis, or both, should be monitored with oximetry or complete polysomnography.

Pharmacotherapy. Several drugs have been advocated to use for treatment, but their value is limited in patients with the obstructive sleep apnea syndrome. The most effective and best studied drug is protriptyline hydrochloride, a nonsedating tricyclic agent whose use was found to alleviate abnormal breathing during sleep and to lessen daytime somnolence in four patients with narcolepsy and sleep apnea.[73] In a subsequent study of patients with varying degrees of obstructive sleep apnea, 12 of 14 patients had symptomatic and objective improvement with doses ranging from 2.5 to 25 mg a night.[74] Anticholinergic side effects were frequent, however, resulting in alternative therapy in 50% of patients. In a double-blind crossover study of six patients, the use of protriptyline lessened daytime sleepiness without affecting overall apnea frequency and duration.[75] Smith and associates showed a reduction in apnea frequency and oxygen desaturation during non-REM sleep, as well as a reduction in REM sleep.[76] Of their 12 patients, 10 were subjectively improved, and although side effects were frequent, 11 of 12 tolerated prolonged therapy. The beneficial effect of using protriptyline has been attributed to its suppression of REM sleep and also to a preferential stimulation of upper airway muscle tone.[75,77] Thus, protriptyline offers reasonable prospects for symptomatic improvement and may reduce the degree of oxygen desaturation, but frequent side effects and incomplete efficacy limit its value.

Medroxyprogesterone acetate has been used because of its respiratory stimulant effect and its proved benefit in the obesity-hypoventilation syndrome.[78] In seven patients with the sleep apnea syndrome, however, the use of progesterone did not alter apnea frequency, although oxygenation improved.[79] In another study of eight patients with the obesity-hypoventilation syndrome, improvement occurred in four patients with CO_2 retention but not in the patients with a normal partial pressure of arterial CO_2.[80] Therefore, medroxyprogesterone has limited value in the treatment of obstructive sleep apnea, but it may be effective when the obesity-hypoventilation syndrome with chronic hypercapnia is present.

Acetazolamide, a carbonic anhydrase inhibitor, stimulates respiration by producing a metabolic acidosis. In a group of patients with predominantly central sleep apnea, the use of this drug reduced the number of apneas and improved symptoms.[81] In several cases with mild obstructive apnea, however, acetazolamide administration was associated with more frequent obstructive apneas of longer duration.[82] Thus, the drug is probably not useful in patients with the obstructive sleep apnea syndrome, and we do not use it in these patients.

Miscellaneous adjunctive therapies. Several other adjunctive therapies may be useful in selected patients. The sleep position may affect sleep apnea frequency, with the supine posture resulting in the highest apnea frequency. In some patients, apneas occur only in this position. If these patients can be trained to sleep on their side, sleep and breathing may be substantially improved,[83] but the feasibility of this approach for long-term care remains to be proved. Another report suggests that moving from the recumbent to a sitting posture can bring immediate improvement.[84] Severely affected patients often sleep in a chair because of this side

effect, but the benefit is marginal because the improvement of sleep and breathing is incomplete. Medical therapy for nasal obstruction due to allergic or vasomotor rhinitis may be helpful, but its effects in patients with the sleep apnea syndrome has not been studied.

Evaluation

Selecting one or several of the above therapies hinges on a careful evaluation of patients. The probability of diagnosis, the degree of disability, etiologic factors and the potential for various therapies should all be considered in doing a history and physical examination, sleep studies and adjunctive tests (Figure 1). The history should not only investigate symptoms of disturbed breathing during sleep and its consequences, but should also develop the relationship of these symptoms to age, weight, sleeping position, the use of alcohol or medications and any other medical history. Because patients may be unaware of the events at night and may say they are not sleepy during the day, an interview with a spouse or some other observer is important. In our experience, however, the obstructive sleep apnea syndrome usually produces symptoms that by themselves are not specific but in the aggregate produce a strong clinical impression of the diagnosis. Snoring, arousals from sleep with choking or gasping, spouse-observed apneas and pathologic sleepiness in passive or monotonous circumstances are usually present and occur more frequently than in normal subjects. Carefully assessing pathologic sleepiness is essential, as this is the principal consequence of obstructive sleep apnea, and we use this symptom to classify the severity of the disease. Occasionally, the sleep apnea syndrome produces a complaint of insomnia, but in our experience, this complaint is usually accompanied by symptoms of abnormal breathing during sleep.

Physical examination of a patient should include a thorough general examination. Measurement of height and weight, blood pressure, careful assessment of lung and cardiac function and an assessment of the neuromuscular system are all relevant to the diagnosis of this disease. In addition,

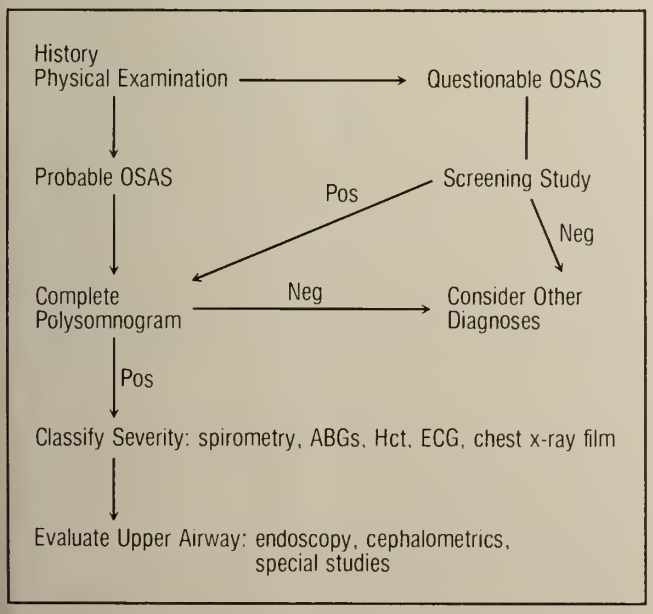

Figure 1.—The schema shows the process for evaluating patients for the obstructive sleep apnea syndrome (OSAS). ABGs = arterial blood gas determinations, ECG = electrocardiogram, Hct = hematocrit

examination of the upper airway is critical. The facial appearance often provides a clue to a maxillary or mandibular deficiency. The mouth and throat should be examined for a gross pathologic condition, including malocclusion, tonsillar hypertrophy, a long uvula and redundant pharyngeal mucosal folds. Special consideration should be given to the relative size of the oral cavity and tongue. The position of the soft palate relative to the posterior pharyngeal wall may give some indication of the potential for occlusion. Although most patients with the obstructive sleep apnea syndrome do not have striking anatomic abnormalities, the throat often appears "crowded" and the oropharyngeal airway appears small.

The next step in the evaluation is an objective evaluation of breathing in sleep. If by history the probability of the sleep apnea syndrome is low, we recommend a screening test using one of several home monitors or, for inpatients, an all-night recording of oxygen saturation during sleep. If a reasonable probability of the syndrome can be established by the initial interview, however, or if the screening test is positive, a complete polysomnogram should be done. Polysomnography is the current standard for diagnosis because it defines the problem in all its dimensions: sleep disturbance, respiratory disturbance including apneas and hypopneas, oxygen desaturation, cardiac arrhythmia and sleep position.

When the sleep apnea syndrome is confirmed, more detailed examinations are necessary to assist the selection of therapy. A fiber-optic examination of the airway is helpful in assessing the site of obstruction and may help predict those patients most likely to respond favorably to surgical treatment.[24] We have patients execute the Mueller maneuver, although interpreting this maneuver is difficult. If the facial appearance suggests a skeletal abnormality, a lateral cephalometric radiograph is done.

Additional examinations include an assessment of cardiopulmonary function. Spirometry, arterial blood gas determinations, hemoglobin concentration, electrocardiography and chest x-ray films all serve to evaluate the presence of coexistent lung disease, respiratory failure and cor pulmonale. A 24-hour Holter monitor may be appropriate if polysomnography has identified cardiac arrhythmias other than the typical sinus variation. In view of the frequency of thyroid disease in the general population and the high prevalence of sleep apnea in hypothyroid patients,[85] a routine assessment for hypothyroidism and treatment if results are abnormal appear justified. Consideration of other endocrine disorders should be based on physical findings.

Classification—Therapeutic Recommendations

After a complete examination, it is useful to classify the severity of disease by a combination of clinical and polysomnographic criteria (Table 2). In addition to conventional polygraphic indicators of breathing in sleep, we consider the extent of sleep fragmentation—that is, the frequency of periodic respiration-related arousals—and periodic breathing, defined by stereotypic periodic desaturations on a compressed recording of oxygen saturation. The criteria for classification are arbitrary but correspond approximately to current symptoms and disability. Treatment is then based on the severity of disease (Table 3). The importance of tailoring the treatment to each patient cannot be overemphasized. Factors such as age and other medical conditions influence the choice of therapy. A frail, elderly person may present an unacceptable surgical risk. On the other hand, a younger patient may find long-term

TABLE 2.—*Obstructive Sleep Apnea Syndrome: Classification of Severity*

Variable	*Mild*	*Moderate*	*Severe*
Sleep Data			
Sleep	Mostly normal; <25% of sleep fragmented	Some consolidated sleep present, no stage 3 or 4	Totally fragmented
Breathing, % periodic	<50	50-90	>90
Apneas			
Number/h	<20	<40	>40
Duration, s	<20	<30	>30
O_2 saturation, %			
Mean	>90	>85	<85
Lowest	>80	CO_2 partial pressure normal; no heart failure	Elevated CO_2 partial pressure, hematocrit; cor pulmonale, heart failure

CO_2 = carbon dioxide, ECG = electrocardiogram, O_2 = oxygen

TABLE 3.—*Therapy for the Obstructive Sleep Apnea Syndrome*

Mild	*Moderate*	*Severe*
		Tracheostomy
	Nasal CPAP	Nasal CPAP
	UPPP	
	Other surgical therapy, such as maxillofacial, gastroplasty	Other surgical therapy, such as maxillofacial, gastroplasty
Drugs: protriptyline hydrochloride	Drugs: protriptyline hydrochloride	
Prostheses		
Oxygen, weight loss, no alcohol or sedation	Oxygen, weight loss, no alcohol or sedation	Oxygen, weight loss, no alcohol or sedation

CPAP = continuous positive airway pressure, UPPP = uvulopalatopharyngoplasty

nasal CPAP therapy unacceptable and may prefer a surgical alternative.

All patients with sleep apnea are instructed to avoid using respiratory depressants such as alcohol, narcotics and sedatives. Avoidance of sedatives is particularly important with surgical treatment. We do not administer sedatives preoperatively until a patient is in the operating suite, and after an operation we observe the patient in the intensive care unit for the first 24 hours.

Patients with severe disease show extreme pathologic sleepiness and respiratory failure. Because they are at risk for sudden death,[6] the choice of treatment should be nasal CPAP or tracheostomy, the two treatments that have the greatest likelihood of immediate success. An ancillary operation such as uvulopalatopharyngoplasty or other surgical procedures may be included along with the primary forms of therapy and, if successful, may eventually allow the patient to have a tracheostomy closed or nasal CPAP discontinued. Significant weight loss in obese patients may likewise eliminate the need for long-term tracheostomy or nasal CPAP, after some time.

Patients with moderate obstructive sleep apnea complain of sleepiness but do not have respiratory failure and their disability is limited. The long-term prognosis of these patients is unclear, and treatment must be tailored to each person. Tracheostomy is usually not justified medically or acceptable to the patient. Assessing the upper airway may reveal obstruction that can be corrected surgically. The biggest problem, however, is the common situation of a moderately impaired patient whose airway may not be obviously correctable. Uvulopalatopharyngoplasty may be offered but only as a procedure with a significant chance of failure. Newer surgical procedures are not sufficiently evaluated to define their role. As a result, nonsurgical therapy is a major consideration. Nasal CPAP is likely to be efficacious but will not be acceptable to all patients. The use of protriptyline, oxygen therapy and prosthetic devices should be considered. Weight loss should be a part of every regimen.

Mild sleep apnea may be quite subtle. Sleepiness is minimal and medical complications are not present. As with moderate sleep apnea, the prognosis is not known, and treatment must be individualized. Surgical treatment is generally not recommended unless there are other associated problems such as nasal obstruction or favorable findings such as enlarged tonsils. Weight reduction is appropriate in most patients. The use of protriptyline or other pharmacologic therapy may be helpful.

All patients require follow-up. Because therapies are not always effective, every treated patient must be reevaluated to assure that the desired clinical result has been achieved. In most cases, this evaluation will require some objective assessment of breathing in sleep. Because the clinical experience with sleep apnea is short and the experience with many therapies is shorter and because the prognosis for patients cannot be predicted with certainty, all should be reevaluated periodically to identify progression of disease or relapses after successful treatment.

Conclusion

The obstructive sleep apnea syndrome is a disorder characterized by abnormal breathing during sleep and manifests a wide range of severity. The treatment selected must be based on a thorough evaluation of the patient and assessment of the severity of disease and then tailored to the individual patient according to the relative risks and benefits of the therapy. The efficacy of the therapy chosen should be monitored both subjectively and objectively. Controlled prospective clinical trials are needed to better evaluate the various treatment options available.

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Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

Trauma in Children

Edited by Randall E. Marcus, MD, Coordinator of Trauma Services and Assistant Professor of Orthopedic Surgery, Case Western Reserve University School of Medicine, and Attending Orthopedic Surgeon, Rainbow Babies and Children's Hospital, Cleveland. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 265 pages, $54.

Trauma in Children is a 265 page, one volume book edited by Randall Marcus with 20 other contributors. The chapters discuss trauma in children by anatomic regions including the head and central nervous system, chest, abdomen, genito-urinary region, hand, spine and face. There are also chapters on fractures, soft tissue injuries and complications of musculoskeletal injuries, as well as introductory chapters on initial management and general principles of trauma management in children. The last two chapters of the book address psychological and legal implications of trauma.

Each chapter is an independent discussion of a topic by professionals with personal experience in the field. In general, each chapter provides an overview with more extensive discussions of the common or serious injuries. The depth of discussion varies among chapters but generally is fairly superficial. Someone desiring to understand current management of a specific fracture, for instance, would find a much more complete discussion of the topic in a specialty text.

There are some distracting editorial shortcomings such as mislabeled figures. There are very few pictorial examples of long-term followup or even final results of fracture treatment, an important consideration in pediatric fractures. Omissions occur in other chapters. For instance, there is no mention of child abuse in the chapter "Legal Considerations in the Treatment of Trauma in Children."

The specific topic of trauma in children has not been well addressed previously in book form in this country. This book is a good survey of pediatric trauma and crosses the conventional boundaries of medicine. It would be of value to someone who occasionally deals in pediatric trauma who would like to become familiar with some of the current concepts. It would also be of value to the trauma subspecialist to introduce the principles of treatment of pediatric trauma in other disciplines or anatomic regions.

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Clinical Review

Clinical Disorders of Phosphorus Metabolism

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Deranged phosphorus metabolism is commonly encountered in clinical medicine. Disturbances in phosphate intake, excretion and transcellular shift account for the abnormal serum levels. As a result of the essential role played by phosphate in intracellular metabolism, the clinical manifestations of hypophosphatemia and hyperphosphatemia are extensive. An understanding of the pathophysiology of various phosphate disorders is helpful in guiding therapeutic decisions.

(Yu GC, Lee DBN: Clinical disorders of phosphorus metabolism. West J Med 1987 Nov; 147:569-576)

In human tissues phosphorus exists in both organic and inorganic forms. Organic phosphorus comprises the phospholipids, nucleic acids and phosphoproteins that are needed for cellular integrity and metabolism. Intracellular inorganic phosphorus provides substrate for the synthesis of energy-generating compounds including adenosine triphosphate (ATP). Serum phosphorus is mostly in inorganic forms consisting of orthophosphate ions. In adults the normal serum phosphorus level ranges from 3.0 to 4.5 mg per dl. The human body contains about 600 to 700 grams of phosphorus, of which 80% to 85% is found in bone, 10% to 15% in soft tissue and only about 1% in the extracellular fluid (ECF).[1] In normal persons, the serum phosphorus level undergoes a diurnal variation of as much as 1.5 mg per dl, with the nadir between 8 AM and noon and the peak between 2 AM and 6 AM.[2] These fluctuations are likely the result of meals and a circadian rhythm of parathyroid hormone secretion.

The average dietary phosphorus intake varies from 800 to 1,200 mg per day. The percentage of dietary phosphorus absorbed by the intestine remains remarkably constant at 60% to 65% over a wide range of phosphorus intake (4 to 30 mg per kg per day).[3] Thus, the dietary intake of phosphorus is an important determinant of the amount of phosphorus absorbed. In addition, phosphate absorption is regulated by vitamin D, mainly through the action of its active metabolite, 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D_3). Phosphorus is present in most food, especially red meat, dairy products, fish, poultry and the legumes. Phosphorus is absorbed as phosphate ions from the intestinal lumen and distributed in the ECF. From the ECF, phosphates are handled by two general processes: an intracellular-extracellular shift and renal excretion. The absorbed phosphate is first "buffered" by shifting into the soft tissue cells (and probably also the skeleton). In time, any excess phosphate is ultimately excreted by the kidneys. Shifts of phosphate between extracellular and intracellular compartments cause immediate changes in the serum phosphorus level without changes in the total phosphorus balance. Renal phosphate excretion is determined by the difference between phosphate filtered at the glomerulus and phosphate absorbed by the tubule. Normally about 85% of the filtered phosphate is reabsorbed by the tubule and the remaining 15% is excreted in the urine.[4] The maximal tubular phosphate reabsorptive capacity (TmP) plays a major role in maintaining a long-term, steady-state serum phosphorus concentration—that is, the higher the TmP, the higher the serum phosphorus concentration. The total body phosphorus balance is maintained by urinary excretion of the excess phosphate absorbed by the intestine. In a person who is in phosphorus balance, the urinary phosphate concentration would equal the phosphate absorbed. Factors that may influence renal phosphate reabsorption are listed in Table 1.

Hypophosphatemia and Phosphorus Depletion

The terms hypophosphatemia, phosphorus deprivation and phosphorus depletion should be differentiated. Hypophosphatemia simply means a serum phosphorus concentration below the range found in a normal population. Phosphorus deprivation is generally used to indicate selective omission of phosphorus from the diet, sometimes accompanied by the administration of intestinal phosphate binders. Phosphate depletion denotes a state in which the body phosphorus store is actually reduced. The distinction between phosphorus deprivation and phosphorus depletion is important because many biochemical changes attributed to phosphorus depletion in fact develop within hours of removing phosphorus from the diet—that is, long before an appreciable net phosphorus loss from the body can occur.

Starvation leads to a catabolic state with loss of water, nitrogen, potassium, phosphorus and magnesium in the same proportion as in the tissues. The phosphorus content of the remaining tissue would therefore be normal for the reduced body mass. Thus hypophosphatemia is not a feature of starvation per se.

Sustained hypophosphatemia encountered in clinical practice generally represents conditions with an abnormally reduced TmP, rather than phosphorus deprivation or depletion. Hypophosphatemia associated with ample phosphate in the urine suggests an abnormally low TmP as the cause for the reduced serum phosphorus concentration. A reduced TmP can be caused by excessive parathyroid hormone secretion or by intrinsic tubular transport defects. In such conditions, a total body phosphorus balance may still be maintained and phosphorus depletion may not develop. The laboratory characteristic of phosphorus deprivation and phosphorus depletion is hypophosphatemia associated with the virtual absence

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ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
AMP = adenosine monophosphate
ATP = adenosine triphosphate
cyclic AMP = adenosine 3′:5′-cyclic phosphate
ECF = extracellular fluid
GFR = glomerular filtration rate
PTH = parathyroid hormone
TmP = maximal tubular phosphate reabsorptive capacity

of phosphate in the urine.[5] There are exceptions, however. Conditions associated with an accelerated intracellular phosphate shift, such as respiratory alkalosis and insulin administration (vide infra), may also show diminished urinary phosphate excretion. Hypophosphatemia associated with these conditions is clearly not the result of phosphorus deprivation or phosphorus depletion.

Causes of Hypophosphatemia and Phosphorus Depletion

Hypophosphatemia may result from three general mechanisms. They are increased phosphate shift into cells and bone, decreased intestinal phosphate absorption or increased intestinal loss of phosphate and inappropriate urinary phosphate loss through a reduction in the renal phosphate reabsorptive capacity.[6] Chronic, stable hypophosphatemia of moderate severity—serum phosphorus level 1.5 to 2.5 mg per dl—is generally caused by a reduction in the maximal renal phosphate reabsorptive capacity and does not manifest characteristics of the phosphorus depletion syndrome. Severe hypophosphatemia—serum phosphorus level less than 1.5 mg per dl—on the other hand, is often associated with phosphorus deprivation or depletion and may be accompanied by clinical manifestations of the phosphorus depletion syndrome.[7] It is obvious, however, that hypophosphatemia does not always indicate phosphorus depletion. Figure 1 summarizes the hypophosphatemic disorders encountered in clinical practice.

TABLE 1.—*Factors Influencing Renal Handling of Phosphates*

- Decreased renal phosphate absorption
  - Hormonal
    - Parathyroid hormone
    - Glucocorticoids
    - Sex hormones
    - Calcitonin
    - Thyroid hormone
  - Metabolic
    - High dietary phosphate intake
    - Metabolic acidosis
    - Alcoholism
    - Urinary alkalinization
  - Diuresis
    - Diuretics
    - Osmotic
    - Extracellular fluid volume expansion
- Increased renal phosphate absorption
  - Hormonal
    - Insulin
    - Vitamin D metabolites
    - Growth hormone
  - Metabolic
    - Dietary phosphate restriction
    - Hypercalcemia
    - Hypermagnesemia

Hypophosphatemia Associated With Other Mineral Disorders

Increased phosphate shift into cells and bone. The most common cause of acute hypophosphatemia in inpatients is the intravenous administration of carbohydrate, usually glucose. The reduction in serum phosphorus concentration is usually modest and transient. Fructose administration, on the other hand, may lead to a more prolonged and pronounced decrease in the serum concentration of phosphorus.[8] This is due to the intracellular trapping of phosphate as fructose 1-phosphate. The lack of negative feedback by the end-product fructose 1-phosphate on the enzyme fructokinase allows for the continual cellular uptake of phosphate. Severe hypophosphatemia may develop, especially in those with congenital fructose intolerance.

The nutritional recovery syndrome was first observed during rapid refeeding of severely malnourished prisoners of war. The modern equivalent of this syndrome can be seen in the intravenous feeding of patients with severe debilitation or anorexia nervosa, especially if the hyperalimentation solutions are deficient in phosphates.[9] The anabolic state from refeeding promotes an intracellular shift of phosphate and may lead to severe hypophosphatemia, frequently associated with hypokalemia and hypomagnesemia.

Respiratory alkalosis is a common cause of moderate to severe hypophosphatemia.[10] Hyperventilation-induced hypocapnia leads to a secondary reduction of intracellular carbon dioxide and an increase of intracellular pH, which activates phosphofructokinase. This results in accelerated glycolysis, and the enhanced glucose phosphorylation promotes transcellular phosphate influx. Salicylate overdose and gram-negative sepsis are thought to cause hypophosphatemia through respiratory alkalosis. In addition, the massive release of catecholamines with sepsis also promotes cellular uptake of phosphate.[11]

Rapid tumor growth may cause hypophosphatemia by increasing the phosphate demand for cell proliferation and growth, especially in patients with lymphomas.[12] The underlying mechanism of hypophosphatemia was thought to be rapid tumor growth and the high intracellular phosphate content of a lymphoblast compared with a mature lymphocyte.

The "hungry bone syndrome" is a rare disorder in which

Conditions	Altered Phosphate Metabolism: Increased Transcellular Shift	Decreased Intestinal Absorption	Reduced Renal Reabsorption
Carbohydrate load	—		
Nutritional recovery syndrome and hyperalimentation*	—		
Respiratory alkalosis	—		
Rapid cell growth*	—		
Hungry bone syndrome*	—		
Selective dietary phosphorus deprivation*		—	
Administration of phosphate-binding antacids*		—	
Vomiting		—	
Prolonged nasogastric suction		—	
Severe malabsorption disorders		—	
Hyperparathyroidism			—
Primary renal tubular disorders			—
Secondary renal tubular disorders			—
Acidosis	—		—
Severe burns*	—		—
Gout	—		—
Sodium lactate administration	—		—
Abnormal vitamin D metabolic states		—	—
Oncogenic hypophosphatemia		—	—
Hemodialysis*		—	—
Diabetic ketoacidosis*	—	—	—
Alcoholism*	—	—	—
Postrenal transplantation	—	—	—

Figure 1.—Clinical conditions associated with hypophosphatemia: the role of the three major pathophysiologic mechanisms. —denotes the mechanism(s) responsible for hypophosphatemia in a given clinical condition, *denotes conditions that may cause severe hypophosphatemia and phosphorus depletion

hypophosphatemia develops as a result of therapy, leading to rapid new bone formation in a severely demineralized skeleton. This may follow a subtotal parathyroidectomy in a patient with primary or secondary hyperparathyroidism.

Decreased absorption or increased loss of phosphate in the intestine. Because of the universal presence of phosphate in food, a selective dietary phosphorus deficiency is generally achieved only under experimental conditions. Certain aluminum- and magnesium-containing antacids avidly bind to intestinal phosphate and render it nonabsorbable. When this condition is superimposed on poor oral intake, vomiting or prolonged nasogastric suction, severe hypophosphatemia may result. Malabsorptive disorders per se rarely cause significant phosphorus depletion.

Reduced maximal renal phosphate reabsorptive capacity. Hyperparathyroidism is a common cause of moderate hypophosphatemia. The parathyroid hormone (PTH) reduces the renal phosphate reabsorptive capacity and leads to a low serum phosphorus level. Primary renal tubular disorders associated with hypophosphatemia include renal tubular acidosis and the renal Fanconi syndrome.[13] The conditions that lead to secondary renal tubular dysfunction and renal phosphate wasting are depicted in Figure 1.

Both increased intracellular phosphate shift and decreased renal phosphate reabsorptive capacity. Acidosis induces decomposition of intracellular organic compounds with release of inorganic phosphate, which is subsequently excreted in the urine.[1] Hypophosphatemia generally develops during the treatment of acidosis from resynthesis of organic compounds and intracellular shift of inorganic phosphate.

A severe burn injury may also induce hypophosphatemia.[14] The lowest serum phosphorus level is commonly seen on the fifth day. The hypophosphatemia may last from two to ten days. Possible mechanisms include respiratory alkalosis from gram-negative sepsis and pain as well as rapid tissue rebuilding. These patients also have an inappropriate phosphaturia in the presence of severe hypophosphatemia, suggesting a defect in renal tubular phosphate reabsorption.

The hypophosphatemia of untreated gout has been attributed to respiratory alkalosis produced by pain-induced hyperventilation and a reduction in renal phosphate reabsorption due to tubular damage.[7,15]

Sodium lactate infusion promotes phosphaturia through volume expansion. In addition, volume expansion leads to a decrease in serum calcium levels, causing release of the parathyroid hormone, which in turn reduces renal phosphate reabsorption. Lactate infusion also increases hepatic glucose production and the consequent intracellular phosphate shift.[1]

Reduced renal phosphate reabsorptive capacity and decreased intestinal absorption of phosphate. Hypophosphatemia, renal phosphaturia and impaired intestinal absorption of calcium and phosphate are common features of vitamin D-deficient, -dependent and -resistant rickets or osteomalacia.[1]

Oncogenic hypophosphatemia is an interesting entity associated with mesenchymal tumors.[16] The underlying mechanism is unclear but may be related to an increased sensitivity to the phosphaturic effect of PTH, a reduced level of 1,25-dihydroxyvitamin D_3 or the production of an unknown phosphaturic agent.

Severe hypophosphatemia has been described in patients receiving dialysis and attributed to a combination of phosphate loss through dialysis and the intensive use of phosphate-binding antacids.[17]

Increased intracellular phosphate shift and reduction in both renal phosphate reabsorptive capacity and intestinal absorption of phosphate. In clinical practice, severe hypophosphatemia is often seen in patients recovering from diabetic ketoacidosis and from alcoholic withdrawal. Patients with diabetic ketoacidosis often have decreased phosphate intake from anorexia, nausea and vomiting before being admitted to hospital. Concomitant metabolic acidosis enhances the breakdown of intracellular organic phosphates, and the catabolic effects of insulin deficiency promote a phosphate shift into the ECF, leading to increased phosphaturia. Glycosuria and ketonuria induce a further renal phosphate loss. Before treatment, despite normal or even increased serum phosphorus levels, these patients have a total body phosphorus deficit. During treatment, administering insulin promotes glycolysis and oxidative phosphorylation with a rapid shift of phosphates into the cells. In addition, vigorous fluid replacement may enhance renal phosphate excretion. Usually 6 to 12 hours following the initiation of therapy for diabetic ketoacidosis, the serum phosphorus level may fall precipitously.

Another clinical setting in which severe hypophosphatemia often arises is in a patient admitted to hospital with chronic alcoholism.[18] The patient may have decreased phosphate intake from a poor diet or vomiting. Steatorrhea and malabsorption due to chronic pancreatitis and alcoholic cirrhosis may lead to vitamin D deficiency and a resultant hyperparathyroidism. Both conditions lead to increased renal and intestinal loss of phosphates. In addition, concomitant alcoholic ketosis, hypokalemia and hypomagnesemia may promote further renal phosphate clearance.[19,20] During hospital stay, nutritional repletion with intravenous administration of a glucose solution will lead to increased cellular phosphate uptake. This transcellular phosphate shift is further enhanced by respiratory alkalosis from alcohol withdrawal, hepatic encephalopathy or concomitant sepsis. The use of phosphate-binding antacids to treat gastrointestinal bleeding or of lactulose further aggravates hypophosphatemia. Severe hypophosphatemia can typically develop 24 to 72 hours after hospital admission.

Hypophosphatemia may be seen in a third of patients following a renal transplant.[21] A reduced renal phosphate reabsorptive capacity is an important contributing factor. The possible mechanisms for renal phosphate wasting include persistent hyperparathyroidism, subnormal graft function, corticosteroid and diuretic therapy and chronic volume expansion. The use of phosphate-binding antacids for peptic ulcer prophylaxis leads to a decreased intestinal absorption of phosphate. In addition, the resolution of hyperparathyroidism coupled with an increase in circulating 1,25-dihydroxyvitamin D_3 associated with the recovery of renal function may promote healing of renal osteodystrophy with a rapid and sometimes profound skeletal influx of calcium and phosphorus. In some chronically malnourished uremic patients, a posttransplant anabolic state may promote a further intracellular shift of phosphate for soft tissue synthesis.

Clinical Consequences of Severe Hypophosphatemia and Phosphorus Depletion

Multiple organ dysfunction may occur as a result of severe hypophosphatemia and phosphorus depletion. These disturbances from hypophosphatemia commonly occur in patients with chronic debilitation, often in a setting of preexisting cellular injury.

The clinical sequelae of severe hypophosphatemia and phosphorus depletion are the result of three critical biochemical disturbances.[22] First, the level of 2,3-diphosphoglycerate in erythrocytes is decreased, leading to increased oxygen affinity of the hemoglobin and a resultant tissue hypoxia. Second, there is a decrease in the intracellular concentration of ATP, the energy source needed for cell functions. Third, inorganic phosphate is a crucial cofactor in the glyceraldehyde-phosphate-dehydrogenase step of the Embden-Meyerhof pathway, and a deficiency of intracellular inorganic phosphate may impair glycolysis.

The critical determinants of cellular injury appear to be the level of inorganic phosphate and adenine nucleotide in the cytosol.[23] When cytosolic ATP decreases below a critical level, cellular dysfunction or necrosis may ensue. The cytosolic inorganic phosphate is essential for the formation of ATP from adenosine diphosphate (ADP). In addition, intracellular inorganic phosphate has an important role in determining the cellular pool of adenine nucleotides. Normally, ATP, ADP and adenosine monophosphate (AMP) are related by the following reaction:

$$2\,\mathrm{ADP} \rightleftharpoons \mathrm{AMP} + \mathrm{ATP}$$

A major degradation pathway for AMP is the irreversible deamination to inosine monophosphate through the action of AMP-deaminase. This enzyme is inhibited by a normal intracellular phosphate concentration. Therefore, a significant reduction in intracellular inorganic phosphate may result in AMP degradation and a decrease of the total adenine nucleotide pool. In addition, a drop in ATP concentration enhances the action of 5′-nucleotidase, which further reduces the amount of nucleotides. Any demand in energy production may place the cell in jeopardy of disintegrating from a further decrease in intracellular ATP concentration.

The various systemic dysfunctions in severe hypophosphatemia and phosphate depletion are summarized in Figure 2.

Experimental evidence points to a significant impairment of the cardiovascular system in patients with severe hypophosphatemia. An increased cardiac index was found in critically ill hypophosphatemic patients given phosphorus replacement.[24] A decreased myocardial stroke work was also found in dogs with chronic phosphorus deficiency.[25] Decreased vascular reactivity to angiotensin II and norepinephrine has been shown in phosphorus-depleted animals.[26]

Acute respiratory failure from respiratory muscle weakness is a serious complication of severe hypophosphatemia. Reversible hypophosphatemia-induced diaphragmatic weakness and pulmonary insufficiency have been shown.[27] Hypophosphatemia may induce hyperventilation, possibly the result of poor tissue oxygenation from decreased erythrocyte 2,3-diphosphoglycerate levels. Hyperventilation leads to respiratory alkalosis and a further lowering of the serum phosphorus level. The vicious cycle may finally induce hypoventilation due to respiratory muscle fatigue.

Various neurologic manifestations may follow phosphorus depletion. Severe hypophosphatemia can result in a metabolic encephalopathy with paresthesia, tremor, ataxia, weakness, irritability, confusion, seizure and eventually coma.[28] This has been shown in patients receiving phosphate-deficient hyperalimentation and could be prevented with adequate phosphate supplementation.

Muscle biopsies from hypophosphatemic persons with alcoholism have shown a decrease in cellular phosphorus and an increase in intracellular sodium, chloride and water. This may account for the generalized weakness or proximal myopathy seen in some hypophosphatemic patients. Severe hypophosphatemia may induce rhabdomyolysis with elevated serum creatine kinase levels.[29] This is usually asymptomatic or clinically mild. Occasionally profound weakness, muscle pain and acute myoglobinuric renal failure may develop.

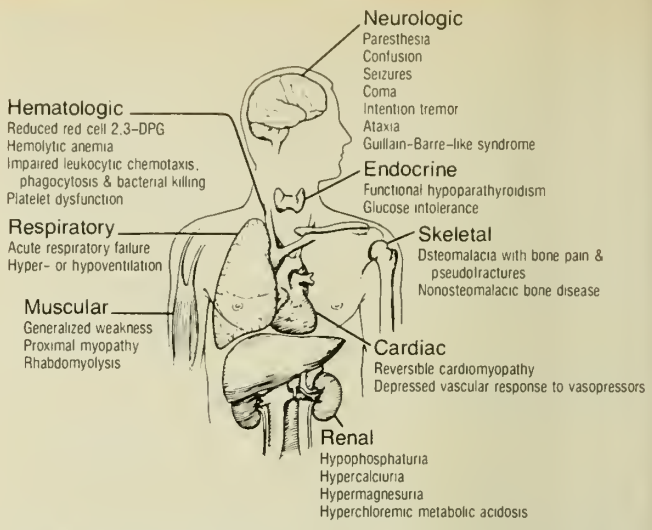

Figure 2.—The clinical manifestations of severe hypophosphatemia and phosphorus depletion are shown. 2,3-DPG = 2,3-diphosphoglycerate

Hemolytic anemia is a rare complication of phosphorus depletion but may occur when serum phosphorus values fall below 0.5 mg per dl.[30] Such a drop in the serum phosphorus level leads to a decrease in intracellular inorganic phosphate in erythrocytes. This in turn leads to impaired glycolysis with a fall in intracellular ATP. The elasticity of the red cell membrane is maintained by a microfilament system dependent on ATP for energy sources. Therefore, insufficient ATP may cause erythrocyte rigidity and may lead to fragmentation in the microcirculation. Another important biochemical consequence of hypophosphatemia in erythrocytes is the drop in 2,3-diphosphoglycerate, which leads to a leftward shift in the hemoglobin-oxygen dissociation curve. The increased oxygen binding by erythrocytes will result in a decreased peripheral oxygen delivery and tissue hypoxia.[31]

Experimental studies have shown defects of chemotaxis, phagocytosis and bacterial killing in leukocytes of hypophosphatemic animals. This may be related to impaired microtubular actions from low cellular ATP levels and abnormal membrane synthesis.[32]

Thrombocytopenia, decreased platelet survival and impaired clot retraction have been shown in animals with induced hypophosphatemia.[33] These may be due to a reduction of platelet ATP content. Similar clinical findings have not been observed in humans, however.

Metabolic acidosis may also result from severe hypophosphatemia by three mechanisms.[34] First, a decrease in titratable acid excretion follows hypophosphaturia. Second, a fall in renal ammonia excretion due to hypophosphatemia leads to decreased acid excretion. Third, renal tubular bicarbonate reabsorption may be reduced, which can lead to a hyperchloremic metabolic acidosis. Clinically the degree of acidosis is usually mild as a result of skeletal buffering from mobilization of both phosphorus and bicarbonate. Severe metabolic aci-

dosis, however, has been observed in hypophosphatemic malnourished children receiving hyperalimentation.[34] This may be related to defective mobilization of skeletal buffers.

A state of functional hypoparathyroidism exists in patients with severe hypophosphatemia and phosphorus depletion.[35]

Diagnostic Approach

Generally the cause of hypophosphatemia is apparent from the history or clinical setting under which it occurs. Measuring the urinary phosphorus concentration is helpful in difficult cases.[36] A fractional phosphate excretion of less than 10% or a 24-hour phosphorus output of less than 100 mg should lead to a search for causes other than renal phosphate wasting. Such patients may have a transcellular phosphate shift, an increased nonrenal loss or a decreased phosphate intake or absorption. A transcellular phosphate shift is the most common cause of hypophosphatemia in an inpatient.

Renal phosphate wasting is suggested by a urinary fractional phosphate excretion of greater than 20% or a 24-hour phosphorus output of more than 100 mg in the presence of hypophosphatemia. An associated increase in urinary glucose, amino acid, bicarbonate and uric acid levels points to the renal Fanconi syndrome as the underlying disease. Measuring serum calcium and PTH levels will distinguish hyperparathyroidism from the other causes of renal phosphate leak.

Treatment

At normal body pH (7.40), serum phosphorus exists in two forms, $H_2PO_4^-$ and $HPO_4^=$. Their relationship can be expressed by the following chemical reaction:

$$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^=$$

The relative proportion of these ions in the serum can be calculated from the Henderson-Hasselbalch equation:

$$pH = pK + \log [HPO_4^=]/[H_2PO_4^-]$$

Because normal serum pH is 7.40 and the physiologic pK is 6.80, we have:

$$7.40 = 6.80 + \log [HPO_4^=]/[H_2PO_4^-]$$

or

$$0.60 = \log [HPO_4^=]/[H_2PO_4^-]$$

And antilog 0.60 = 4, therefore:

$$[HPO_4^=]/[H_2PO_4^-] = 4$$

or

$$[HPO_4^=] = 4\,[H_2PO_4^-]$$

Because the orthophosphate ions are expressed in a molar concentration in the Henderson-Hasselbalch equation, the molar ratio of $HPO_4^=$ to $H_2PO_4^-$ is 4:1 under normal serum pH. A solution containing the two orthophosphate ions in the above ratio will have a pH of 7.40 and is commonly called a "neutral phosphate" solution.

It follows that in normal serum, every 5 mmol per liter of serum phosphate contains 4 mmol per liter of divalent phosphate and 1 mmol per liter of monovalent phosphate, giving a total of 9 negative charges per 5 phosphate ions, or a valence of 9/5 = 1.8. Therefore, the interconversion of serum phosphate from millimoles to milliequivalents at normal serum pH is 1 mmol = 1.8 mEq.

It is also apparent that changes in pH will affect the ratio of the phosphate ions and thus alter the concentration of the solution expressed in mEq per liter. To avoid confusion, all therapeutic phosphate preparations should be expressed in mmol per liter and elemental phosphorus in mg per dl because these concentrations are independent of pH. Each mmol per liter of phosphate contains 3.1 mg per dl of elemental phosphorus.

Modes of Therapy

Asymptomatic moderate hypophosphatemia usually only requires attention to the underlying cause. For hyperalimentation solutions, the addition of 15 mmol per liter of phosphate will normally prevent hypophosphatemia. The judicious use of phosphate-binding antacids in patients with peptic ulcer disease or chronic renal failure will avoid hypophosphatemia. For patients with respiratory alkalosis, treatment of the underlying disorder—sepsis, acute gout or metabolic encephalopathy—will reverse the hypophosphatemia.

Treatment of hypophosphatemia in diabetic ketoacidosis remains controversial.[37] Despite normal or elevated levels of serum phosphorus before treatment, these patients become hypophosphatemic and hypophosphaturic when given fluids and insulin. Clinical manifestations of severe hypophosphatemia usually do not develop, however, and serum phosphorus levels normalize when oral intake is resumed. In addition, several studies have failed to show a decreased insulin requirement or degree of acidosis, improved glucose metabolism or decreased erythrocyte abnormalities with phosphate supplementation. Nonetheless, the small proportion of patients who present with hypophosphatemia before treatment require close monitoring. They have significant phosphorus depletion, and severe hypophosphatemia is likely to develop during therapy for diabetic ketoacidosis. These patients may benefit from phosphate administration.

Patients with chronic alcoholism, on the other hand, frequently have phosphorus depletion at the time of admission to hospital. Frequent monitoring of their serum phosphorus levels is indicated. Phosphate supplementation may be given when an evolving trend toward hypophosphatemia becomes clear, so that a full-blown phosphorus-depletion syndrome may be aborted.

For patients with severe hypophosphatemia associated with clinical manifestations of phosphorus depletion, therapy should be instituted without delay. As a general rule, oral therapy is preferred unless the patient cannot tolerate oral feeding or has severe hypophosphatemia with life-threatening complications.

Skim milk has about 1 gram per liter of both phosphorus and calcium. It is a safe and desirable form of phosphorus supplementation. If a patient cannot tolerate lactose or a substantial fluid intake, a commercial phosphate preparation may be used. A total daily amount of 2 to 3 grams of elemental phosphorus may be given in two to four divided doses. Mild diarrhea is a frequent side effect. Various commonly available phosphate preparations are listed in Table 2.

For patients requiring parenteral administration of phosphate, caution must be exercised to prevent hyperphosphatemia. The volume of distribution of the administered phosphate has wide individual variation and is affected by the serum pH, glucose and insulin availability. In addition, phosphorus-depleted patients have pronounced hypophosphaturia and may continue to have it for some time despite correction of their hypophosphatemia. Consequently, they are vulnerable to the development of hyperphosphatemia when a large quantity of phosphate is given parenterally over a short period of time. We recommend that no more than 1 gram of ele-

mental phosphorus be given by steady infusion over 24 hours. In patients with renal failure or oliguria, potassium phosphate preparations should be avoided. An initial phosphate dose of 0.08 mmol per kg body weight (2.5 mg per kg body weight) may be given over six hours.[38] The dose may be increased to 0.16 mmol per kg (5.0 mg per kg) if a patient has serious life-threatening clinical manifestations. Thereafter, serum levels of phosphorus, calcium, potassium and magnesium should be determined and the rate of phosphate infusion adjusted accordingly. Parenteral phosphate infusion should be discontinued when the serum phosphorus level is greater than 2 mg per dl or a serum calcium level is less than 8 mg per dl.

The hazards of parenteral phosphate therapy include hyperphosphatemia, hypocalcemia, hypomagnesemia, metastatic calcification, hypotension and renal failure.[39] Diuresis may accompany phosphate administration and lead to dehydration, hypokalemia and hypernatremia. Patients with renal failure receiving parenteral phosphate therapy are especially susceptible to serious complications.

Hyperphosphatemia

Hyperphosphatemia is a frequent laboratory finding in inpatients. There are several mechanisms accounting for the increase in serum phosphorus (Table 3). By far the most common cause is from decreased renal phosphate excretion. This is generally a result of decreased glomerular filtration from renal insufficiency but may also result from an increased renal tubular phosphate reabsorption in patients without renal failure. A substantial increase in phosphate intake may lead to severe hyperphosphatemia, especially with uremic patients. Further, a large extracellular phosphate load may be a result of a transcellular phosphate shift or cell lysis. Finally, several causes for spurious elevations of serum phosphorus levels have been reported. These include specimens that have undergone prolonged refrigeration or delay before a phosphorus measurement, hemolysis, contamination with heparin sodium or detergents and the presence of hyperbilirubinemia, dysproteinemia or hyperlipidemia.[40]

In patients with chronic renal failure, the fractional excretion of phosphate by the remaining nephrons is increased, sometimes as much as 90% of a filtered load.[41] This degree of phosphaturia by individual nephrons is important in maintaining a normal serum phosphorus level in the presence of a decreasing glomerular filtration rate (GFR). But when the GFR is less than 25 ml per minute and if dietary phosphate intake is not reduced proportionately, the serum phosphorus level will rise. In turn, the filtered phosphate load will increase with a corresponding rise in phosphate excretion. A new phosphorus balance will then be established at a higher serum phosphorus level.

The parathyroid hormone is an important regulator in the renal excretion of phosphate.[42] Patients with hypoparathyroidism have diminished urinary adenosine 3′:5′-cyclic phosphate (cyclic AMP) production and increased renal tubular phosphate reabsorption. The serum phosphorus level in these patients ranges from 7 to 9 mg per dl.[43] Patients with idiopathic hypoparathyroidism tend to have higher serum phosphorus levels than those with surgical hypoparathyroidism. These patients also have hypocalcemia, which predisposes them to tetany and seizures.

In pseudohypoparathyroidism there is an end-organ resistance to the effect of parathyroid hormone.[44] These patients have hyperphosphatemia and hypocalcemia, and the PTH level is usually elevated. Patients with type I pseudohypoparathyroidism have low urinary cyclic AMP and phosphate

TABLE 2.—*Commonly Available Phosphate Preparations**

Preparations	*Phosphorus Content, 1 gram*	*Sodium, mEq†*	*Potassium mEq†*
Oral			
Skim milk	1,000 ml	28	39
Neutra-Phos‡	300 ml or 4 capsules	28	28
Neutra-Phos K‡	300 ml or 4 capsules	0	57
Phospho-Soda§	6.2 ml	57	0
K-Phos Neutral‖	4 tablets	50	5
K-Phos Original (Sodium Free)‖	7 tablets	0	26
Parenteral			
Hyper-Phos-K¶	15 ml	0	50
Sodium phosphate	11 ml	45	0
Potassium phosphate	11 ml	0	45

*Adapted from Lee et al.[1]
†Content in 1 gram of phosphorus
‡Willen Drug Company, Baltimore.
§C. B. Fleet Company, Inc, Lynchburg, Va.
‖Beach Pharmaceuticals, Tampa, Fla.
¶Abbott Laboratories, North Chicago

TABLE 3.—*Common Causes of Hyperphosphatemia*

- Decreased renal phosphate excretion
  - Decreased glomerular filtration rate
    - Renal failure, chronic and acute
  - Increased tubular reabsorption
    - Hypoparathyroidism
    - Pseudohypoparathyroidism, types I and II
    - Acromegaly
    - Hyperthyroidism
    - Etidronate disodium
    - Tumoral calcinosis
- Increased phosphate intake
  - Oral or intravenous administration of phosphate
  - Phosphate-containing laxatives or enemas
  - Vitamin D intoxication
  - White phosphorus burns
- Increased extracellular phosphate load
  - Transcellular shift
    - Lactic acidosis
    - Respiratory acidosis
    - Untreated diabetic ketoacidosis
  - Cell lysis
    - Rhabdomyolysis
    - Malignant hyperpyrexia
    - Intravascular hemolysis
    - Cytotoxic therapy
    - Leukemia
    - Lymphoma
    - Acute intestinal ischemia
- Spurious hyperphosphatemia
  - Prolonged refrigeration of specimen or delay in measuring
  - Heparin sodium contamination
  - Traumatic hemolysis
  - Hyperbilirubinemia
  - Dysproteinemia
  - Hyperlipidemia
- Miscellaneous
  - Volume contraction
  - Familial intermittent hyperphosphatemia
  - Cortical hyperostosis

excretion with exogenous PTH administration. Those with type II pseudohypoparathyroidism have high urinary cyclic AMP but low phosphate excretion when given exogenous PTH. Therefore, PTH resistance can be proximal (type I) or distal (type II) to the production of cyclic AMP. In addition, certain physical anomalies may exist in patients with pseudohypoparathyroidism. These include short stature, round face, short neck, shortening of the metacarpals and subcutaneous calcifications.

Mild hyperphosphatemia may be seen in a third of patients with hyperthyroidism.[45] This is due to increased bone resorption and renal tubular phosphate reabsorption.

Acromegaly is also associated with hyperphosphatemia through an increased renal phosphate reabsorption induced by growth hormone.

The diphosphonate, etidronate disodium, is useful for treating Paget's disease. The hyperphosphatemic effect is dose-dependent and may be related to a decreased renal phosphate excretion and a transcellular phosphate shift.[46]

Tumoral calcinosis is a rare syndrome seen in young black men.[47] Patients have ectopic calcifications around large joints with associated hyperphosphatemia and normal serum calcium and PTH levels. The soft tissue calcification is due to an increased calcium-phosphate product. The pathogenesis may be enhanced renal tubular reabsorption of phosphate and calcium.

Metabolic acidosis is often associated with hyperphosphatemia. A breakdown of organic phosphate with a release of inorganic phosphate into the extracellular fluid is the likely explanation. Lactic acidosis tends to cause a greater degree of hyperphosphatemia than diabetic ketoacidosis under a similar pH.[48] This may be due to concomitant tissue hypoxia and a further transcellular phosphate shift in patients with lactic acidosis.

In rhabdomyolysis the release of intracellular phosphate stores with muscle necrosis in a setting of acute renal failure may lead to severe hyperphosphatemia.[49] Cytotoxic therapy for lymphoblastic leukemia and Burkitt's lymphoma also leads to the release of high intracellular phosphate loads into the extracellular space.[50]

Malignant hyperpyrexia is a rare complication of general anesthesia, and hyperphosphatemia may occur independent of rhabdomyolysis and acute renal failure.[51]

Clinical Manifestations

The clinical consequences of hyperphosphatemia are related to its effects on serum calcium, PTH and skeletal and soft tissues. Severe hyperphosphatemia is often associated with hypocalcemia, especially when the serum phosphorus level rises rapidly. The possible underlying mechanisms include soft tissue calcium-phosphate salt deposition, reduced bone resorption and reduced 1,25-dihydroxyvitamin D_3 formation. Symptomatic hypocalcemia may develop, leading to tetany and seizures.

Soft tissue calcification is common in hyperphosphatemic patients with chronic renal failure, hypoparathyroidism and tumoral calcinosis. The normal calcium-phosphate product is 40 mg^2 per dl^2 (10 mg per dl calcium × 4 mg per dl phosphate). The in vitro solubility product of calcium and phosphate is 58 mg^2 per dl^2. In humans, metastatic calcification is likely when this product exceeds 70 mg^2 per dl^2. Calcification may occur in the heart, blood vessels, lungs, cornea, kidneys and gastric mucosa. The alkaline intracellular milieu of the lungs, cornea, kidneys and gastric mucosa may enhance calcium-phosphate salt deposition.

Hyperphosphatemia and hypocalcemia in patients with chronic renal failure often lead to hyperparathyroidism. The elevated PTH level is an important factor in the pathogenesis of renal osteodystrophy. In addition, high PTH levels aggravate soft tissue calcification and may produce calciphylaxis with subcutaneous tissue necrosis. Experimental evidence also implicates a causal role for PTH in the pruritus and anemia of uremia.[52]

Treatment

The principles of the treatment of hyperphosphatemia are in reducing phosphate intake and promoting phosphate excretion.

In patients with normal renal function, increased phosphate intake rarely produces significant hyperphosphatemia. In hyperphosphatemia due to chemotherapy for leukemia or lymphoma, vigorous saline diuresis will lead to increased phosphaturia. Alternatively, the administration of acetazolamide, 500 mg every six hours, will enhance renal phosphate excretion through urinary alkalinization and natriuresis.[53]

In patients with chronic renal failure, restricting dietary phosphate intake to 600 to 900 mg per day can maintain normal serum phosphorus levels, provided that the GFR is greater than 30 ml per minute. When the GFR is less than 25 ml per minute, a phosphate binder will be needed. Aluminum hydroxide and aluminum carbonate liquid gels—Amphojel, Basaljel (Wyeth Laboratories, Philadelphia)—are the commonly used drugs.[54] These antacids bind to the intestinal phosphates (from both exogenous intake and endogenous secretion from the parotid glands and pancreas) and render them nonabsorbable. The usual dosage is 20 to 40 ml one hour after each meal and at bedtime. Calcium carbonate has recently been shown to normalize serum phosphorus levels in patients undergoing long-term dialysis.[55] These patients ingest an average of 8.5 grams of calcium carbonate per day (range 2.5 grams to 17 grams). The long-term side effects, such as metastatic calcification, will need to be determined.

In addition, dietary phosphate intake should be kept to less than 1 gram per day to avoid a positive phosphorus balance and to minimize the dosage of antacid needed. Nausea is a frequent side effect with the ingestion of aluminum-containing liquid gels. Desiccated gels in the form of capsules or tablets—Alu-Cap, Alu-Tab (Riker Laboratories, St Paul)—may be substituted. The dried gels have less phosphate-retaining power, however. Long-term ingestion of large quantities of aluminum-containing phosphate binders may lead to aluminum bone disease in patients on dialysis. Magnesium-containing antacids should not be used in patients with renal failure, as a decreased renal clearance of ingested magnesium will lead to magnesium intoxication.

Calcium supplementation and vitamin D metabolites are also given to dialysis patients to increase the serum calcium concentration and reduce the severity of secondary hyperparathyroidism. Hemodialysis may remove substantial extracellular phosphate and lower serum phosphorus levels transiently. Equilibration with intracellular phosphate stores, however, will restore the serum phosphorus to predialysis levels in a few hours. In patients with chronic renal failure and intractable hyperphosphatemia, a subtotal parathyroidectomy may be considered to reduce the mobilization of phosphorus from skeletal stores.

In patients with hypoparathyroidism, calcium and vitamin D supplementation are generally prescribed to correct hypocalcemia, although these patients have increased urinary calcium excretion as a result of their low PTH levels. Increasing serum calcium levels to the normal range may predispose them to nephrolithiasis. Serum calcium levels should also be monitored frequently to avoid vitamin D intoxication.

The therapy for tumoral calcinosis is dietary calcium and phosphorus restriction. The use of phosphate binders may be added. A negative calcium and phosphorus balance in these patients will lead to reductions in soft tissue calcification.

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'Moderate' Hypophosphatemia—Not Always an Innocent Bystander

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As pointed out by Drs Yu and Lee in their consideration of hypophosphatemia, severe hypophosphatemia that reflects severe cellular depletion of phosphate is that clinical instance of hypophosphatemia generally considered to demand careful monitoring and sometimes phosphate replacement therapy. Clearly, cellular depletion of phosphorus can profoundly impair tissue metabolism and function.[1] But in most clinical instances the measured severity of hypophosphatemia alone does not indicate whether a clinically important tissue disorder will occur, which tissue (or tissues) will be affected or whether phosphate therapy will be useful.

Apart from the fact that the measured severity of hypophosphatemia provides little indication as to the severity or distribution of tissue depletion of phosphate, the usually measured morning fasting value of serum phosphate can substantially underestimate the severity of hypophosphatemia that occurs throughout most of the day. As Yu and Lee point out, a diurnal variation in the serum concentration of phosphate occurs in normal subjects under normal metabolic conditions: a decrease in the morning to a nadir shortly before noon, followed by a rapid increase to an extended plateau in the afternoon and a modest further increase to a peak shortly after midnight. Using spectral analysis, Portale and associates found that in normal men the normal diurnal variation in serum levels of phosphorus can be described as the sum of sinusoidal functions with periodicities of 24 and 12 hours.[2] Dietary restriction of phosphorus, combined with orally administered aluminum hydroxide, induced within ten days striking changes in the character of the diurnal rhythm of serum phosphate: Although inducing only a modest decrease in the morning fasting value of serum phosphate, this combination abolished the 12-hour periodic component of the time series that normally includes the afternoon rise in serum phosphate and thus induced a 40% reduction in the 24-hour mean serum level of phosphorus. Accordingly, the magnitude of reduction in the serum level of phosphorus induced at 0800 was only half that induced throughout the afternoon, the values decreasing to 2.6 and 2.0 mg per dl, respectively. Even with phosphorus restriction, the nocturnal peak in phosporus concentration was present in each subject, if at a lower level—that is, the 24-hour periodicity was maintained. Phosphorus supplementation for ten days that induced no persisting change in its morning fasting level induced a 14% increase in the 24-hour mean serum level of phosphorus by exaggerating the early afternoon rise in serum phosphorus.

Within ten days, restriction and supplementation of dietary phosphorus induced striking changes in the plasma concentration of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D), an 80% increase and 30% decrease, respectively, changes entirely accounted for by changes in the production rate of 1,25-dihydroxyvitamin D.[3] The changes induced in the 24-hour mean serum level of phosphorus varied inversely and significantly with those induced in the production rate (and plasma concentration) of 1,25-dihydroxyvitamin D ($r = -.88$, $P < .001$). Thus, modest diet-induced reductions in the morning fasting serum level of phosphorus are predictably attended by later, larger reductions in serum phosphate that probably mediate the observed large increases in the production rate and plasma concentration of 1,25-dihydroxyvitamin D.

1,25-Dihydroxyvitamin D is the most active metabolite of vitamin D known with respect to stimulating not only intestinal absorption of phosphate and calcium but also bone resorption.[4] At least in part by stimulating bone resorption, administered 1,25-dihydroxyvitamin D increases the plasma concentration of phosphate in phosphate-depleted vitamin D-deficient rats, when intestinal absorption of phosphate is negligible and renal reabsorption of phosphate virtually complete.[5] Even moderate hypophosphatemia enhances bone resorption in the rat, and the effect is mitigated by vitamin D deficiency.[6] Severe hypophosphatemia inhibits bone matrix formation and mineralization. These hypophosphatemic skeletal phenomena do not require parathyroid hormone.

These facts bear directly on the hypophosphatemic syndrome induced in humans over time by phosphate-binding antacids such as aluminum hydroxide. As described clinically and induced experimentally in human subjects by Lotz and colleagues,[7] this syndrome is characterized biochemically by severe hypophosphatemia, the near disappearance of urinary phosphate, striking hypercalciuria that is caused in part by bone resorption and greatly increased values of serum alkaline phosphatase. It has generally been held that the symptoms and signs of this syndrome—muscle weakness, bone pain, malaise, anorexia and rickets or osteomalacia—do not occur without severe hypophosphatemia. But as judged from the published descriptions of a number of those affected, clinically important, phosphate-responsive disorders of bone and muscle can result from antacid-induced hypophosphatemia that is not severe, at least as traditionally measured in the morning fasting state.[8-11] In all reported cases of the syn-

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drome, with one notable exception,[8] the values of serum phosphorus reported are either morning fasting values or their timing is not specified. In the index case of antacid-induced, phosphate depletion-dependent metabolic bone disease and myopathy, a woman self-medicated with aluminum hydroxide, Bloom and Flinchum were at pains to point out that whereas the morning fasting value of serum phosphate was hardly reduced at 2.9 mg per dl, the afternoon value was distinctly reduced at 2.0 mg per dl and repeatedly so for as long as aluminum hydroxide use was continued.

Of further note, only careful questioning elicited this patient's history of having ingested large amounts of aluminum hydroxide for many years. Even when discontinuance of the use of this substance had stopped her bone pain, ameliorated her muscle weakness and effected a general state of physical rejuvenation, she still "missed her 'stomach medicine.'" Given that aluminum hydroxide can readily relieve and prevent the pain of a chronic disorder, it is perhaps not surprising that many become habituated to this substance and are reluctant to be forthcoming about its abuse.

Of particular interest are two recently described cases of antacid-induced, histomorphometrically documented osteomalacia in men who complained only of incapacitating bone pain and both denying having had muscle weakness, malaise or anorexia.[9,10] Neither had severe hypophosphatemia, as measured by their morning fasting values of serum phosphate, 3.2 and 2.0 mg per dl, respectively. But in both, urinary phosphate was negligible and the plasma concentrations of 1,25-dihydroxyvitamin D were extremely high, more than twice the upper limit of the normal range; the values of urinary calcium and plasma alkaline phosphatase were greatly increased. It seems likely that in both men the mean 24-hour concentration of serum phosphate was much lower than the morning fasting value. As might have been predicted, in both men, discontinuing the use of antacid, combined with dietary supplementation of phosphorus, rapidly stopped the bone pain, healed the osteomalacia, and reduced to normal values the plasma concentration of 1,25-dihydroxyvitamin D, urinary calcium and plasma alkaline phosphatase.

Moderate hypophosphatemia induced by the use of phosphate-binding antacids can also give rise to phosphate-responsive proximal myopathy and rheumatic phenomena unassociated with apparent osteomalacia.[12]

The question can be raised as to whether the phosphate-responsive syndrome of metabolic bone disease or myopathy requires not only chronic hypophosphatemia but also the long-term ingestion of aluminum hydroxide. Clearly, aluminum can be absorbed from the gut in amounts that impair normal bone metabolism and formation. In a particularly pristine instance of chronic moderate hypophosphatemia, the recently described hereditary hypophosphatemic rickets with hypercalciuria (HHRH),[13,14] an apparently isolated impairment in the renal reabsorption of phosphate accounts for all the attendant metabolic abnormalities through the single agency of chronic hypophosphatemia. In addition to metabolic bone disease, these abnormalities include greatly increased plasma concentrations of 1,25-dihydroxyvitamin D and muscle weakness as well as hypercalciuria,[13,14] none of which occur in patients with X-linked hypophosphatemic rickets.[15] In further distinction, in patients with HHRH, continued phosphate therapy *alone* readily induces normal serum concentrations of phosphate and 1,25-dihydroxyvitamin D and, within months, the disappearance of both the bone pain and radiographic signs of rickets and the acceleration of linear growth in those children whose growth plate has remained open. Phosphate therapy alone also rapidly improves muscle strength and normalizes the urinary excretion of calcium and the serum value of alkaline phosphatase.

Thus, in humans, chronic moderate hypophosphatemia per se, as traditionally determined from measurements made in the morning fasting state, gives rise to metabolic bone disease, myopathy and persisting, large increases in the plasma concentrations of 1,25-dihydroxyvitamin D. Because the increased plasma concentration of 1,25-dihydroxyvitamin D probably contributes to the metabolic bone disease in the hypophosphatemic state by mobilizing bone mineral, one might ask what biologic advantage inures to those with hypophosphatemia as a consequence of this humoral response. It has been proposed that bone resorption is enhanced in hypophosphatemia to prevent or attenuate phosphate depletion-dependent dysfunction of the brain and heart.[1,16,17(p3)] In rats fed a diet extremely deficient in phosphorus, bone released large amounts of phosphorus that appeared to be taken up by soft tissues.[16] Tarlo and others have contended that bone originated as a store for mobilizable phosphate, not as a supporting structure.[17] In hypophosphatemic rats that have had thyroparathyroidectomies, the increase in serum phosphate induced by administered 1,25-dihydroxyvitamin D could not be attributed to phosphate mobilized from the heart, kidney, liver, skeletal muscle or diaphragmatic muscle; if anything, tissue phosphate tended to increase in these soft tissues.[5] All of these tissues, as well as brain, appear to be targets for 1,25-dihydroxyvitamin D.[18-21] It is then possible that in clinical states of hypophosphatemia, increased concentrations of 1,25-dihydroxyvitamin D mobilize bone phosphate but act directly on the heart, brain and perhaps other nonskeletal tissues to curtail depletion of their phosphate stores.

Whatever the adaptive, "protective" role of increased plasma concentrations of 1,25-dihydroxyvitamin D in patients with hypophosphatemia, in patients with chronic alcoholism, rhabdomyolysis occurs with moderate hypophosphatemia but is not described in patients with either antacid-induced hypophosphatemia, HHRH or X-linked hypophosphatemic rickets. In otherwise well-nourished dogs that are either chronically intoxicated with ethanol[22] or depleted of magnesium,[23] phosphate depletion occurs in somatic muscle unaccompanied by hypophosphatemia. Chronic alcoholism is frequently attended by magnesium depletion, which not only depletes somatic muscle of phosphate but also promotes renal "wasting" of phosphate.[1] Thus, in a magnesium-depleted person with chronic alcoholism, the somatic muscle is presumably "primed" to be severely injured by an acute hypophosphatemic event, even when the magnitude of hypophosphatemia induced is less than severe. In fact, in patients selected for their acute alcoholic myopathy, the total muscle phosphorus and magnesium values were invariably reduced and the serum concentrations of phosphate and magnesium were frequently reduced, but the values in serum bore little relationship to those in muscle.[24] The fact, then, of severe hypophosphatemia signals the possibility of a metabolically significant, clinically important cellular depletion of phosphate, but such depletion often occurs without it, particularly in the specific instance of chronic alcoholism. Of interest in this regard is a recent report of phosphate-responsive recurrent ventricular tachycardia in a group of only moderately hypophosphatemic patients without evident organic

heart disease, but in whom chronic alcoholism was the major illness and in whom chronic phosphate depletion could be inferred.[25] Similarly, in two of four recently described cases of chronic alcoholism and acute respiratory failure, the induction of only moderate hypophosphatemia, by abruptly correcting an abnormally increased arterial partial pressure of carbon dioxide, was attended by an impairment of diaphragmatic contractility that was rapidly responsive to phosphate replacement therapy.[26]

The clinical point, of course, is that certain clinical states of "moderate" hypophosphatemia, particularly as judged by morning fasting values of the serum phosphate, can be pathogenetic of serious clinical disorders that are dramatically responsive to phosphate therapy. Two such clinical states are chronic abuse of aluminum hydroxide and chronic abuse of ethanol.

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Medical Staff Conference

Advances in the Prenatal Diagnosis of Sickle Cell Anemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

MARC A. SHUMAN, MD*: *Presenting this Medical Staff Conference is Stephen Embury, MD. Dr Embury is Chief of the Hematology Service at San Francisco General Hospital, and his particular areas of investigative interest are sickle cell disease and thalassemia. He has both a clinical and a research interest in these areas, as he provides clinical care for the adult patients with sickle cell anemia enrolled in the Northern California Sickle Cell Center and he conducts research on the molecular biology and genetics of abnormal globin genes. Dr Embury came to the University of California, San Francisco (UCSF), in 1977 to work in the laboratory of Yuet W. Kan, MD. That was an exciting time in that laboratory because the very next year Dr Kan published his landmark paper describing the use of DNA analysis for the antenatal diagnosis of sickle cell disease. Since that time there have been several significant advances in the area of prenatal diagnosis, and recently Dr Embury has contributed to this field with an article in the* New England Journal of Medicine.

STEPHEN H. EMBURY, MD†: Thank you very much, Marc. In this Medical Staff Conference, I will review several salient advances that have been made in the approach to the prenatal diagnosis of sickle cell anemia. Methods to be discussed will span from the initial chromatographic analysis of fetal blood through recently developed techniques of DNA analysis that, because of their simple and rapid nature, have the potential for more widespread applications in the medical community. In these initial comments I would like to acknowledge the important contributions of three local persons to this field. Drs Y.W. Kan and Mitchell Golbus of UCSF have made seminal and continuing contributions, as has Dr Blanche Alter from Mount Sinai Hospital in New York, who is currently spending her sabbatical leave at UCSF. Several excellent reviews have discussed recent advances in prenatal diagnosis.[1-5]

The clinical complications of sickle cell anemia are fundamentally related to the poor solubility of sickle hemoglobin (Hb S) when it is deoxygenated. The mutation that is responsible for this insolubility is the substitution of valine for glutamic acid as the sixth amino acid of the β subunit of hemoglobin ($\beta^s = \beta^{val \rightarrow glu}$; Hb S $= \alpha_2\beta_2^s$). This abnormality is inherited in a mendelian codominant fashion, meaning that those persons heterozygous for the gene can be identified but have no clinical morbidity, whereas those homozygous for the mutation have severe clinical disease. According to mendelian genetics, couples in whom both parents are heterozygous for the sickle gene (sickle cell trait, Hb AS) have a 25% chance of conceiving a child homozygous for sickle cell anemia (Hb SS), a 50% chance of having a child with the benign Hb AS condition and a 25% chance of having a normal child without the sickle gene (Hb AA). About 3,000 pregnancies annually in the United States are estimated to be at risk for producing a child with Hb SS, so about 750 conceptions per year result in this genotype. There are now safe and reliable methods of prenatal diagnosis for application in each of these 3,000 pregnancies.

The ideal prenatal diagnostic method would have three important characteristics—diagnostic accuracy, fetal and maternal safety and widespread applicability. The necessity of absolute diagnostic accuracy is underscored by considering the probable decision that results from the prenatal diagnosis of Hb SS—terminating the pregnancy. The importance of maternal and fetal safety is obvious, and there has been an ongoing effort to obtain assayable biologic specimens in a way that does not jeopardize the fetus and that are available early in pregnancy. With the development of techniques that are both reliable and safe, attention has turned to developing techniques that will be more widely available to the medical community, rather than only to specialized research laboratories.

The amino acid substitution responsible for sickle cell anemia also causes a chromatographic difference that allows the β^s subunit of hemoglobin to be distinguished from the β^A subunit,[6] a difference that has been used successfully for prenatal diagnosis in pregnancies at risk for Hb SS.[7] For these studies fetal erythrocytes are obtained during the second trimester either by ultrasound-guided direct placental puncture[7] or by fetoscopy.[8] Fetal reticulocytes in these blood specimens are capable of synthesizing radiolabeled globin chains when the blood is incubated in the presence of radiolabeled amino acids. The different elution patterns of radiolabeled β^A and β^s chains on carboxymethyl chromatography distinguish the Hb AA, Hb AS and Hb SS genotypes. Although this method is accurate, even in the most expert of hands fetal blood sampling resulted in about 5% fetal wastage. Avoiding this risk to fetuses awaited the development of techniques that could detect the sickle mutation at the DNA level.

In the late 1970s much was being learned of the physical organization of human globin genes using blot-hybridization restriction endonuclease mapping. This technique was ca-

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pable of defining the relationship of these genes to each other and identifying gross abnormalities in their structure. The detection, however, of the single nucleotide change causing a structural hemoglobin variant could not be accomplished without the availability of a specific restriction enzyme whose cleavage of DNA was prevented by the nucleotide change. (Alternatively, the nucleotide base change could be detected if it created rather than destroyed a cleavage site.)

An alternate means of identifying DNA mutations was serendipitously discovered by Kan, who found that when genomic DNA was digested with the enzyme *Hpa*I, the normal β^A-globin gene nearly always resided on a fragment of 7.6 kilobases (kb) in length, but that 70% of the time the β^s-globin gene resided on a fragment of 13 kb (Figure 1).[9] It was clear that the GTG→GAG change responsible for the sickle gene[10] was not the cause of this restriction fragment-length polymorphism. Rather, 3′ to the β-globin gene there was a polymorphic *Hpa*I site, the frequency of which differed according to the nature of the adjacent β-globin allele. This polymorphism, thus, was in linkage disequilibrium with the β^A and β^s genes. The inheritance of this polymorphism in a mendelian fashion, the extremely rare occurrence of β^A on the 13-kb fraction and the approximately 70% association of β^s with the 13-kb fragment meant that when family studies could establish linkage of the β^s gene with the 13-kb fragment, linkage analysis could be used for prenatal diagnosis. Thus, in more than 2,000 of the 3,000 pregnancies a year in America that are at risk for Hb SS, the presence or absence of Hb SS can be determined using indirect linkage analysis. This method was, in fact, used successfully for prenatal diagnosis in such a pregnancy.[11]

Indirect linkage analysis is a highly accurate method for prenatal diagnosis for those couples in whom polymorphism linkage has been determined. Moreover, the risk to a fetus is much smaller with a second-trimester amniocentesis than with taking fetal blood specimens.

Two additional considerations of linkage disequilibrium should be mentioned. First, the presence of the sickle gene on restriction fragments of two different lengths suggested that the sickle mutation had occurred more than once during evolution.[12] Second, further analysis of restriction polymorphisms has led to an elaborate taxonomy of polymorphic sites whereby chromosomes bearing a mutant gene can be identified more precisely by the presence of a series of restriction polymorphisms referred to as a haplotype.[13] Analyzing multiple polymorphisms permits the application of indirect analysis to more than 90% of couples at risk for conceiving an Hb SS child.[14]

The next significant breakthrough in sickle cell prenatal diagnosis, direct detection of the mutant nucleotide, was made possible by the availability of the restriction enzyme *Mst*II. As shown in Figure 2, the T for A nucleotide substitution in the sickle gene destroys a *Mst*II site, thereby preventing its digestion in the 5′ portion of the β^s-globin gene.[15-17] The absence of this *Mst*II site from the β^s gene results in the detection of a 1.35-kb *Mst*II fragment rather than the 1.15-kb β^A fragment detected when blot hybridization is done using a 5′-specific β probe. Direct detection of the sickle mutation is accurate, safe and available for the prenatal diagnosis of 100% of pregnancies at risk for Hb SS.[16]

An advance in obstetric technique, obtaining fetal tissue by chorionic villus sampling, has enabled fetal DNA for the sickle gene to be assayed during the first trimester of pregnancy,[19-21] rather than waiting until the second trimester to do an amniocentesis. Thus, DNA analysis can be carried out at a time when maternal-fetal bonding is less well established.

Despite these advances in diagnostic accuracy, general availability and safety, the ability to prenatally diagnose Hb SS has remained the province of a small number of laboratories that have sophisticated technical expertise and a dedication to the field of prenatal diagnosis. More widespread applicability of molecular analysis has awaited the development of methods that are rapid and simple enough to be applied in less specialized laboratories. Important to this goal are two new methods recently developed at the Cetus Corporation (Emeryville, California). Both methods use a technique of enzymatically amplifying in vitro those DNA sequences that contain the target sequences to be analyzed.[22] As shown in Figure 3, 20 nucleotide synthetic primers complementary to genomic sequences that flank the target sequence and reside on oppo-

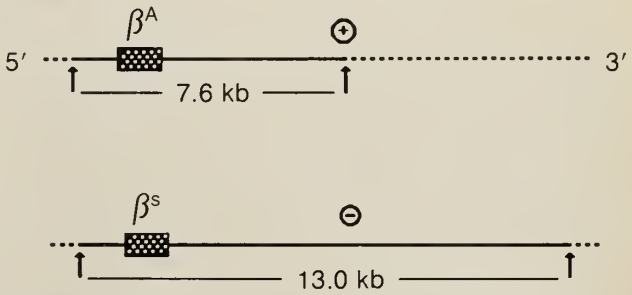

Figure 1.—*Hpa*I polymorphism in linkage disequilibrium is shown with two β-globin alleles, the normal β^A allele on top and the mutant β^s allele or sickle cell gene below. 5′ is on the left and 3′ is on the right. The vertical arrows indicate *Hpa*I cleavage sites. The β^A gene nearly always resides on a 7.6-kilobase (kb) *Hpa*I fragment because the first cleavage site 3′ to the β gene is present (+). Most (70%) of the time the β^s gene resides on a 13.0-kb fragment because the first *Hpa*I site 3′ to the β gene is absent (−) and the next *Hpa*I site is 5.4 kb farther "downstream."

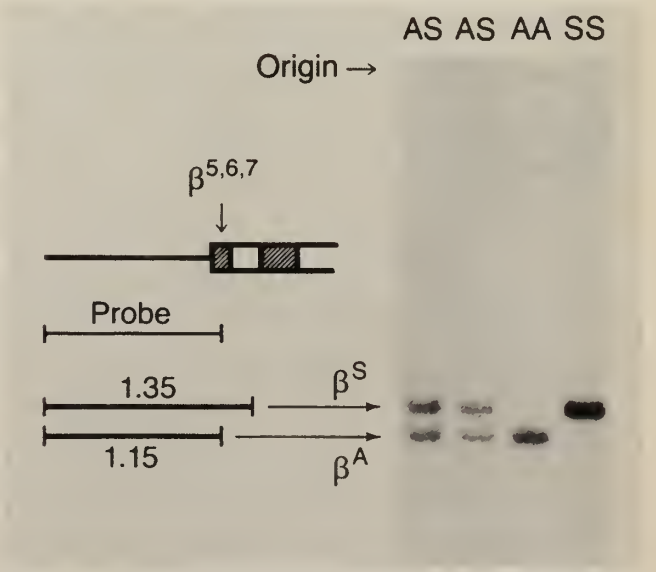

Figure 2.—In this diagram of direct analysis of the sickle mutation by *Mst*II, digestion of the 5′ portion of the β-globin gene is shown. The *Mst*II site involves codons 5, 6 and 7 and is abolished by the presence of the sickle mutation. Use of the indicated fragment as a hybridization probe (Probe) detects a 1.35-kilobase (kb) DNA fragment when the sickle or β^s gene is present and a 1.15-kb fragment with the β^A gene. The autoradiogram on the right shows the diagnostic results from a family with the hemoglobin genotypes indicated above (from Chang et al,[18] with permission).

site DNA strands are hybridized to denatured single-stranded genomic DNA. Each DNA strand is then copied using DNA polymerase to extend these primers in a 5′ to 3′ direction. After each such cycle, the DNA is again denatured and the primers rehybridized so that the recently synthesized DNA strands also serve as a template for the next cycle of DNA synthesis. In this way, the DNA sequences defined by the 5′ end of the primers are amplified exponentially; 20 cycles amplify the target sequences 200,000-fold. Both the sensitivity and specificity of analytic methods are greatly enhanced by amplifying target sequences to this extent, as there is a much larger amount of DNA for analysis and a relative dilution of sequences that are partially homologous and potentially cross-reacting.

In collaboration with the Cetus group, our laboratory successfully used an analytic technique that they had previously described[21] for the prenatal diagnosis of two pregnancies at risk for Hb SS.[23] This analytic method is diagrammed in Figure 4. The β-globin DNA shown on the left in the figure contains the β^A gene and on the right the β^s gene. After the amplified genomic sequences are denatured, they are hybridized with a synthetic 40-nucleotide probe that is radiolabeled at the 5′ end and is perfectly homologous with β^A sequences. The second diagram from the top on the left shows perfect homology of the probe with target sequences, but on the right the DNA duplex formed by β^A probe and β^s target sequences contains an A-A mismatch. The third diagram from the top shows what happens when the two types of duplex are digested with the restriction enzyme *Dde*I, whose cleavage is prevented by the sickle mutation. The perfectly homologous β^A-β^A duplexes on the left yield an eight-nucleotide radiolabeled fragment that dissociates from the duplex due to its short length. The single-base mismatch of the β^A-β^s duplex on the right prevents *Dde*I digestion, and the full-length hybridization probe remains in the duplex. The bottom two diagrams show the result of subsequent digestion with the enzyme *Hinf*I, which also has a recognition site within these duplexes. The radiolabeled eight-nucleotide digestion product on the left is not cleaved by *Hinf*I, as *Hinf*I digests only double-stranded DNA. On the other hand, the β^A-β^s duplex on the right is cleaved by *Hinf*I to yield a three-nucleotide digestion product.

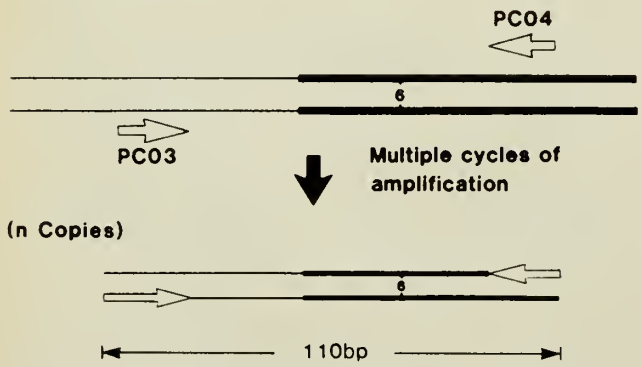

Figure 3.—In this diagram of enzymatic DNA amplification, the upper diagram shows two strands of β-globin DNA (heavy lines) and the relationship of the synthetic primers, PC03 and PC04, that flank the sixth codon of the β-globin gene. The open arrows indicate the primers and the 5′-3′ direction in which they are extended by DNA polymerase. The lower diagram shows the 110-base pair (bp) products obtained by enzymatic DNA amplification. The defined sequences amplified are the genomic DNA between the 5′ end of the primers (from Embury et al,[23] with permission).

Using this method it is possible to distinguish the genotypes Hb AA, Hb SS and Hb AS, as are shown in Figure 5, which contains the results of one prenatal analysis that we did. In the figure, the eight-nucleotide product of lane 1 was generated from amplified DNA of a control subject with the Hb AA genotype, and the three-nucleotide product of lane 2 was generated from amplified DNA of a control subject with the SS genotype. Lanes 3 and 4 contain amplified DNA from maternal leukocytes and second-trimester amniotic cells, respectively. The presence of the eight-nucleotide β^A product and the three-nucleotide β^s product in each verifies their Hb AS genotypes. The pregnancy was allowed to continue, and at term a healthy Hb AS child was delivered.

Previous methods of analyzing genomic DNA with restriction digestion, electrophoresis and blot hybridization required (depending on whether amniocyte culture was necessary) from five days to three weeks to obtain results. With this new technique, results are easily obtained on the day that fetal DNA is available. Because of the ability to amplify small quantities of DNA, it is most unlikely that it will be necessary any longer to do amniocyte culture to obtain greater quantities of DNA.

In being much more rapid and simple than the blot-hybridization method used before, this combination of enzymatic DNA amplification and liquid hybridization restriction analysis brings prenatal diagnosis much closer to the clinical set-

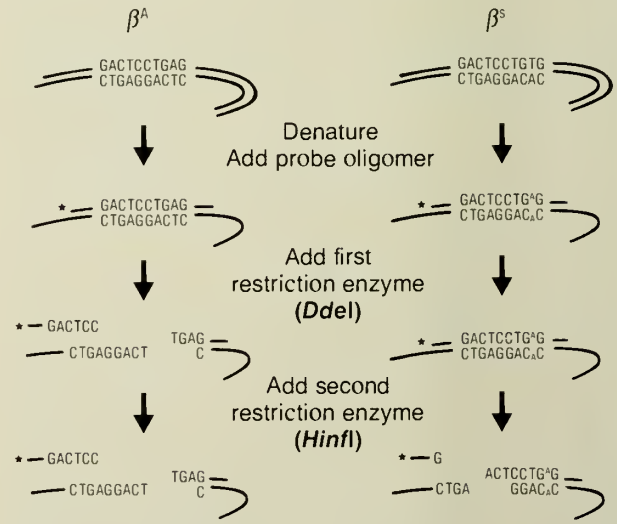

Figure 4.—The steps in liquid hybridization oligomer restriction: The events in analyzing DNA by oligomer restriction with a β^A-specific probe are shown. The diagrams in the left-hand column show the analysis of β^A DNA and the diagrams in the right-hand column the analysis of β^s DNA. In the top two diagrams are shown double-stranded DNA containing the β^A allele and β^s allele, respectively. The two diagrams second from the top show the hybrid duplexes formed by the noncoding strand of denatured DNA and the β^A probe labeled at the 5′ end (★). The duplex containing the β^A noncoding strand is perfectly complementary to the hybridization probe, but the duplex with the noncoding β^s strand contains a single-base A-A mismatch shown by a bubble. The two diagrams third from the top show the results of digesting the duplexes with the restriction enzyme *Dde*I. The duplex with the β^A sequence contains a perfect *Dde*I site, and its cleavage generates a radiolabeled 8-nucleotide product that dissociates from the duplex. The duplex with the β^s target sequences is not cleaved by *Dde*I because of the single-base mismatch. The bottom diagrams show that subsequent digestion with *Hinf*I does not affect the 8-nucleotide cleavage product of β^A, but generates a labeled 3-nucleotide product from duplexes containing β^s target sequences. In this figure, A denotes adenine, C denotes cytosine, G denotes guanine and T denotes thiamine (from Embury et al,[23] with permission).

ting. This technique, however, still requires an electrophoretic step and the use of radioisotopes for labeling the hybridization probe.

Another recently developed method eliminates the electrophoretic step and has been adapted for use with colorimetric rather than radiolabeled hybridization probes.[23] For this method 19-nucleotide allele-specific synthetic hybridization probes[24] are used to hybridize amplified DNA that has been dot-blotted onto nitrocellulose filters. Under stringent hybridization conditions, synthetic 19-nucleotide hybridization probes hybridize only to DNA with which they are perfectly homologous and not to DNA with even a single nucleotide mismatch. Thus, Hb SS DNA hybridizes with a β^s-specific hybridization probe but not a β^A probe; Hb AA DNA hybridizes with a β^A-specific probe but not a β^s probe, and Hb AS DNA hybridizes with both β^A- and β^s-specific probes. Hybridization with allele-specific probes has been detected by labeling the probes with either ^{32}P-nucleotide triphosphates or an avidin-biotin system; this method has also been used to analyze DNA sequences from freshly lysed cells, thus obviating the need for extracting DNA. This approach is equally as fast as the liquid hybridization technique described previously, simpler in that the need for electrophoresis has been eliminated and more readily adaptable for the clinical laboratory due to its potential for avoiding the use of radioisotopes.

It is clear from this discussion that the history of the prenatal diagnosis of sickle cell disease is a rather short one—only 13 years from the use of globin biosynthesis by Kan to the technique of enzymatic DNA amplification and liquid hybridization oligonucleotide restriction that we recently applied. Methods of obtaining biologic samples for assay have also changed. Doing an amniocentesis rather than taking fetal blood specimens in the second trimester remarkably reduced fetal morbidity and mortality. Although the morbidity associated with chorionic villus sampling remains to be determined, this method of obtaining DNA permits prenatal diagnosis in the first trimester rather than waiting until the second trimester when amniocentesis can be done safely. Finally, the technical difficulty associated with detecting the sickle mutation has progressively been reduced. It is clear that advancing from methods requiring biosynthesis studies to direct and indirect DNA analysis by blot hybridization to current methods of analyzing enzymatically amplified DNA has brought us much closer to providing a rapid, simple technique for use clinically. It is conceivable that in the near future physicians in community hospitals will be able to call their clinical laboratory to arrange for the assay of specimens for prenatal diagnosis.

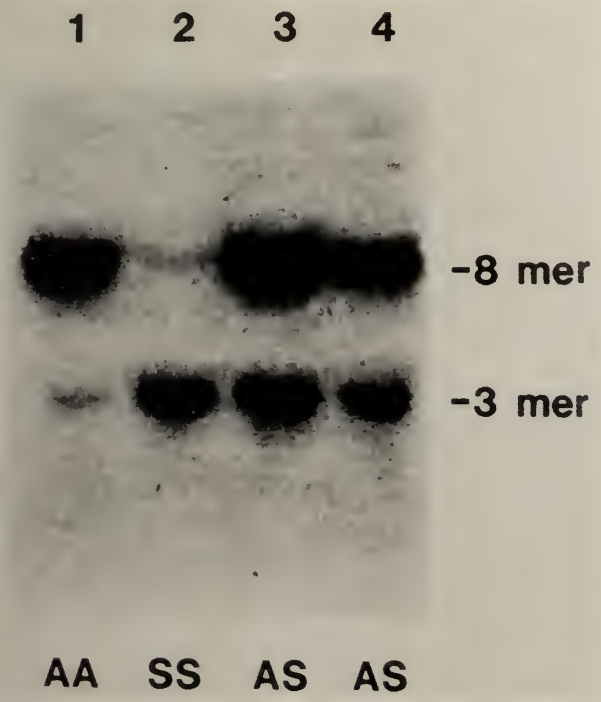

Figure 5.—The autoradiograms show results of enzymatically amplified DNA analyzed by liquid hybridization oligonucleotide restriction, with the amplified control Hb AA DNA in lane 1, control Hb SS DNA in lane 2, Hb AS DNA from maternal leukocytes in lane 3 and fetal DNA obtained from amniotic cells in lane 4. The presence of an 8-nucleotide digestion product (8-mer) indicates the β^A allele and the 3-nucleotide digestion product (3-mer) the β^s allele. The results from amniocyte DNA showed that the fetus had Hb AS (from Embury et al,[23] with permission).

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Epitomes
Important Advances in Clinical Medicine

Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in radiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Angiographic Diagnosis and Therapy for Impotence

UNTIL RECENTLY, impotence was considered largely psychogenic in origin. Following the development of new angiographic methods for diagnosis, it has become apparent that impotence is vasculogenic in at least 50% of patients (63 of 100 in our series). Within our vasculogenic group, 25% had arteriogenic, 37% venogenic and 38% both arteriogenic and venogenic impotence.

A reliable diagnosis requires special angiographic techniques. Arteriography must be done during penile arterial vasodilation, which is usually achieved by intracavernosal injection of 30 to 60 mg of papaverine hydrochloride mixed with 1 mg of phentolamine. Selective internal pudendal arteriography, direct double magnification and nonionic contrast agents are also important adjuncts. Using these refined methods, the dorsal penile and cavernosal arteries—and even the very fine (about 0.25 mm diameter) helicine branches of the cavernosal arteries—are almost always visible in normal persons. Outpatient studies are feasible and enable angiography in a much expanded population. Arteriogenic impotence is diagnosed in the presence of bilateral penile arterial occlusion or significant stenoses.

Cavernosal veno-occlusion is now recognized to be an intrinsic property of normal dilated corpora cavernosa and a necessary prerequisite for erection. Veno-occlusion develops through compression of small subtunical veins by the expanded cavernosal lacunae. The competence of the veno-occlusive mechanism can be evaluated by pharmacomanometry. After the lacunar musculature is fully relaxed by intracavernosal injection of the papaverine-phentolamine mixture, the cavernosal pressure response to an infusion of saline solution or dilute contrast is measured. It is apparent that the normal corpora cavernosa, during erection at systemic cavernosal pressures, leak at a rate of only 2 to 8 ml per minute. Leakage at rates between 20 and 40 ml per minute can contribute significantly to impotence. Leakage at rates above 60 ml per minute, a rate that exceeds potential arterial inflow, constitutes overt venogenic impotence. The routes of leakage can be evaluated by cavernosography.

Preliminary experience suggests that a combination of coils, absorbable gelatin sponge (Gelfoam) and sclerosing agents is effective in obstructing the venous drainage and in enabling return of erectile function. Transcatheter venosclerosis seems to offer several significant advantages over surgical ligation, not the least being the ease with which the deep perforators and their recipient veins can be obstructed, as opposed to the difficulty of surgical access for ligation of these veins. For arteriogenic impotence, arterial bypass procedures will probably be the usual procedure of choice. Occasionally, however, the obstructive disease is anatomically suitable for transluminal angioplasty.

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Duplex Sonographic Diagnosis of Deep Venous Thrombosis of the Leg

DEEP VENOUS THROMBOSIS of the leg is a common disorder and one that is frequently misdiagnosed clinically. Venography has for many years been the gold standard for diagnosis. Nevertheless, concern over possible complications of venography and postmortem studies showing that it is not 100% accurate have led to the development of duplex Doppler sonography to establish the diagnosis.

Duplex real-time sonography combines high-resolution imaging and pulsed Doppler waveform analysis. It has the advantage that it can directly image thrombi and detect abnormal Doppler flow signal. It therefore combines anatomic detail with physiologic evaluation of venous flow. Duplex sonography is comparatively inexpensive, well tolerated, involves no ionizing radiation or contrast material and is not uncomfortable for patients.

Various duplex sonographic findings suggest the diag-

nosis of deep venous thrombosis. The normal deep veins of the leg are readily compressible when light pressure is placed on the ultrasound transducer, and they have a characteristic audible venous "hum" with the Doppler signal. Thrombosed veins are not compressible, and flow is absent. During the Valsalva maneuver, normal major veins distend significantly. The signs of deep venous thrombosis include direct visualization of thrombi, a lack of venous compressibility, an abnormal response to the Valsalva maneuver and an absent or abnormal Doppler venous signal.

In a prospective study comparing duplex Doppler sonography with contrast venography in 54 patients, sonography had a 91% sensitivity for thrombi in the common femoral vein and a 94% sensitivity for thrombi in the superficial femoral or popliteal veins. There were no falsely abnormal examinations. Abnormal Doppler flow and an abnormal response in the common femoral vein to the Valsalva maneuver enabled the detection of thrombi localized to the common femoral or iliac veins.

The main limitation of duplex sonography is its inability to reliably image deep venous thrombosis of the calf. Due to its favorable imaging characteristics and its high reliability, duplex sonography is likely to become a screening method for patients with suspected deep venous thrombosis involving either the common femoral, superficial femoral or popliteal veins.

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Magnetic Resonance Imaging and Pelvic Abnormalities

IN ITS SHORT four-year period of clinical application, magnetic resonance imaging (MRI) has already made a significant impact on the assessment of male and female pelvic abnormalities. The display of pelvic anatomy is unique on MRI: for example, in the male pelvis, it clearly differentiates the zonal anatomy of the prostate; in the female pelvis, it shows both the zonal anatomy of the uterus and changes in the uterine zones during the menstrual cycles. Its greatest contribution, however, has been in evaluating congenital anomalies and male and female infertility and, most importantly, in the staging of pelvic neoplasms. In all three applications, the advantage of MRI lies in its ability to provide direct multiplanar imaging and superb soft-tissue contrast resolution. Magnetic resonance images display a large field of view, and a patient's habitus does not degrade the image.

In the evaluation of congenital anomalies of sexual differentiation, the excellent depiction of the pelvic anatomy on MRI contributes to patient management. In studies of male infertility, MRI shows the presence, size and symmetry of the seminal vesicles, and, through its display of the signal intensity of seminal vesicles, primary or secondary tumors are well visualized. In cases of female infertility, small submucosal leiomyomas, adenomyosis and abnormalities of the corpus uterus or cervix are well displayed.

The most important role of MRI in the pelvis, however, is in the staging of pelvic neoplasms. Its reported accuracy in prostate carcinoma is between 83% and 89%, surpassing that of computed tomography and transrectal ultrasonography. In evaluating bladder tumors, MRI accurately images tumors located at the bladder base or dome and differentiates tumor from surrounding bladder wall hypertrophy or scar tissue—a unique application of this method. In staging endometrial carcinoma, MRI not only displays tumor volume and provides excellent overall accuracy (92%), but also provides an assessment of transmyometrial invasion, which is an important prognostic factor. In cases of cervical carcinoma, tumor location, size, extension and parametrial and sidewall extension are well depicted.

In conclusion, MRI is valuable in assessing pelvic abnormalities and is especially contributory in the staging of pelvic neoplasms.

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Magnetic Resonance Imaging of the Liver

RECENT TECHNICAL AND CLINICAL advances in magnetic resonance imaging (MRI) of the liver have improved image quality and reduced artifacts and imaging times. These advances now make it possible for MRI to challenge computed tomography as the optimal screening method for detecting liver neoplasms.

Artifacts have been reduced by MRI software that incorporates flexible pulse sequence selection, respiratory and cardiac gating, fast scanning techniques, multiple signal averaging and gradient rephasing approaches. While much work still needs to be done before MRI hepatic images are completely free of artifacts, rapid progress is likely to continue.

Recent clinical comparisons between magnetic resonance and computed tomography (CT) in detecting hepatic tumors show that magnetic resonance is better than CT for lesion detectability by 14% and specificity by 9%. A study from the National Institutes of Health showed that magnetic resonance can detect 95% of liver metastases versus 50% for unenhanced CT studies. Thus, it appears to be better than CT for detecting liver lesions and may become the procedure of choice for diagnosing liver metastasis.

Hepatic magnetic resonance contrast agents are being evaluated and hold great promise for detecting liver cancers and for further increasing specificity. Administering intravascular contrast agents such as gadolinium pentetic acid (trisodium zinc diethylenetriaminepentaacetate, DTPA), coupled with new dynamic magnetic resonance techniques, permits the evaluation of tumor vascularity.

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Temporomandibular Joint Radiology Update

MAGNETIC RESONANCE IMAGING (MRI) with small surface coil receivers appears superior to computed tomography (CT) for visualizing the articular discs in both the normal and displaced configurations of the temporomandibular joint. MRI promises to give sufficient detail of the soft tissues of the joint so that using the more invasive positive contrast arthrography may no longer be necessary. Whether or not perforations and tears of the disc can be diagnosed and the state of the bony articular surfaces can be defined still need investigating. Correlative studies need to be done to document the sensitivity and specificity of MRI.

There are still investigative and clinical roles for CT and arthrography. CT may be indicated in communities where MRI is not yet available to screen for disc displacement. In patients with trauma, CT is superior to both conventional radiography and MRI for showing fractures and bleeding. Altered bony joint components and degenerative changes are better seen with CT. Arthrography may be an important test to consider for preoperative evaluation, particularly if CT or MRI findings are equivocal for showing the articular disc. Its ability to show disc movement during function is unsurpassed.

Because of the expense of these sophisticated tests, the significant x-ray exposure from tomograms, arthrography and CT and the current lack of one test to satisfy all diagnostic requirements, the use of these tests must be tailored to each patient. For patients with acute trauma, CT is the first choice. When a clinical evaluation points to disc dislocation, unnecessary x-ray exposure and expense can be avoided by going directly to MRI. A patient with long-standing joint problems may be best examined with CT, particularly if a screening radiograph shows joint deformity.

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Prenatal Diagnosis of Central Nervous System Abnormalities

AS ULTRASOUND image resolution has improved, its role as a low-risk imaging modality for detecting fetal morphologic abnormalities has dramatically increased. Abnormalities of the central nervous system (CNS) have been particularly well studied because the fetal head is routinely imaged in the course of pregnancy dating, CNS abnormalities are relatively common and there is interest in preventing the devastating clinical consequences of many of these abnormalities.

The most common congenital CNS abnormalities are the neural tube defects—anencephaly, encephalomeningocele, myelomeningocele—occurring in aggregate in about 0.2% of births. Anencephaly is readily detectable sonographically from the end of the first trimester onward. Encephalomeningocele and myelomeningocele are detectable by 18 to 20 gestational weeks in most cases. Because 90% of these defects occur sporadically, detecting these abnormalities based on ultrasound screening alone is not practical. Patients with elevated maternal serum or amniotic fluid α-fetoprotein levels constitute a high-risk group for neural tube defect and should be evaluated with high-resolution sonography. The state of California has instituted a statewide maternal serum AFP screening program that should allow detection of the vast majority of neural tube defects.

Fetal cerebral ventricles can be consistently visualized from early in the second trimester. This allows detection of hydrocephalus, which may occur as a result of aqueductal stenosis, the Chiari II malformation associated with myelomeningocele or other causes. Anatomic features usually allow distinction from other causes of dilated cerebrospinal fluid spaces, including hydranencephaly and holoprosencephaly. The posterior fossa can also be well imaged, allowing prenatal diagnosis of the Dandy-Walker malformation.

When ultrasonography detects a definite or possible CNS abnormality, a follow-up examination is frequently useful to further characterize the anomaly, follow progression or plan treatment. In cases of diagnostic difficulty, a second imaging modality—intrauterine magnetic resonance imaging or computed tomography—can be useful. This is necessary in only a small percentage of cases, however.

Because many of these abnormalities are rare, referral to a center specializing in prenatal diagnosis may be indicated. An accurate prenatal diagnosis of CNS abnormalities allows informed patient counseling. This may result in terminating the pregnancy or optimizing obstetric and neonatal care to allow the best possible outcome.

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Percutaneous Gastrostomy

THE ABILITY TO CREATE a gastrostomy by using percutaneous techniques without general anesthesia has simplified patient care. Total parenteral nutrition can frequently be replaced with percutaneous enteral feeding in acutely or chronically ill patients in whom the gastrointestinal tract is intact and functioning. Medical costs can be significantly reduced. Long-term nasogastric feeding is uncomfortable and problems of reflux and esophagitis are common. Percutaneous gastrostomy can largely eliminate the problem of reflux, particularly if the feeding is done in the jejunum.

The stomach is ideally suited for placement of a percutaneous tube because it is a "self-sealing" system. Three layers of interlacing muscular fibers contract around the tube, preventing significant leakage. When a surgical gastrostomy is done, the muscle fibers are cut, and it is therefore necessary to suture the stomach to the anterior abdominal wall to prevent leakage.

Several techniques are available for placing a percutaneous gastrostomy. Using fluoroscopy, the stomach is initially inflated with air and, under fluoroscopic guidance, is punctured with a needle and a guide wire is inserted. A small catheter is placed over the guide wire and, under fluoroscopic guidance, the guide wire is advanced beyond the ligament of Treitz. The tract is then serially dilated and a sheath is placed. A 12 French catheter is advanced over the guide wire and

through the sheath until the tip is beyond the ligament of Treitz.

The endoscopic technique requires the placement of an endoscope in the stomach. A puncture is made and the wire is grasped and removed through the mouth. A long tapered catheter is then fed over the guide wire and exits the anterior abdominal wall at the puncture site. All systems work well with a low rate of complications. The endoscopic technique is somewhat more expensive due to the need for an endoscopy.

A percutaneous gastrostomy can be done on an outpatient basis and, after a short period, oral and enteral feedings can begin. If the gastrostomy is no longer needed, it can simply be removed.

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New Developments in Contrast Media

THREE LOW-OSMOLALITY CONTRAST AGENTS have recently been approved by the Food and Drug Administration. These agents are nonionic media iohexol (Omnipaque, Winthrop-Breon Laboratories) and iopamidol (Isovue, E.R. Squibb & Sons, Inc) and the dimeric media ioxaglate meglumine and ioxaglate sodium (Hexabrix, Mallinckrodt, Inc). These substances differ from the current ionic media in that there is about a third of the osmolality per given iodine concentration (degree of radiographic opacification). Thus, hyperosmolarity-induced reactions to contrast media are lowered with the new agents. Side effects attributable to hypertonicity include hypervolemia; deformity of erythrocytes; damage to vascular endothelium with consequent activation of blood coagulation, the complement system and fibrinolysis; increased release of bradykinin and histamine; cardiac arrhythmias; diuresis; vasodilatation and decreased blood pressure; pain, and heat sensation. All of these reactions are significantly decreased with the new low-osmolality contrast agents.

Contrast media also possess intrinsic molecule-specific properties that may be toxic. When the chemotoxic effects of the new contrast agents are compared with conventional ionic agents, a close correlation exists between systemic toxicity, as measured by the median lethal dose (LD_{50}), and enzyme (acetylcholinesterase) inhibition and protein binding. The protein-binding capacities of contrast agents can be expressed in ratio form as iothalamate: ioxaglate: iopamidol: iohexol = 4:3.5:1.5:1. Iohexol, with the lowest protein-binding capacity and enzyme inhibition, also has the lowest systemic toxicity as measured by LD_{50}. Chemotoxicity may play a role in such side effects as vasodilatation and flushing, bronchospasm and urticaria.

Conventional contrast material can produce acute renal insufficiency. The incidence varies from 0.6% with intravenous procedures to 2% for angiographic procedures. Patients with preexisting renal disease are at increased risk for contrast media-induced nephrotoxicity. The new low-osmolality agents in theory should produce less renal damage. A few reports have shown less renal toxicity, as measured by enzymuria, with iopamidol and iohexol as compared with conventional ionic agents.

The low-osmolality agents have less hemodynamic and electrophysiologic effects when injected into the heart compared with conventional agents. In the pulmonary circulation, the low-osmolality agents produce less elevation of pulmonary artery blood flow and pressure compared with conventional ionic agents.

Iopamidol has been shown to produce half the histamine release of diatrizoate. Nausea and vomiting and urticaria occur more frequently with the use of ioxaglate compared with iohexol and iopamidol. The newer contrast agents have not been used long enough to evaluate the incidence and severity of reactions. In Europe where these agents have been in use longer, there are some data accumulating indicating that rates of minor, moderate and severe reactions are less for nonionic media. Again, the small number of cases limits the conclusions that can be drawn.

At present the new low-osmolality agents are ten times more expensive compared with conventional ionic agents. The new agents should be used selectively in patients known to have an increased risk for reactions.

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Editorials

A Profession Responding to Stress

IN MANY WAYS physicians have been enjoying what many consider to be, or to have been, a Golden Age in medicine. This can be said to have begun during World War II when modern medical science started to come into its own. Since then there has been enormous support for research, professional training and the development of needed resources for health care. American physicians now deliver the best medical care the world has ever seen. But there has been a down side to all this, and the result has been a stressful time for the medical profession. Stated simply, the down side, and, therefore, the present stress, basically derives from the perception by many that the new medical science and technology could assure health for all, and that health care had become too costly and that physicians were somehow responsible for this. Then, there was a concurrent trend toward antielitism, egalitarianism, and revolt against institutional authority. All this happened at more or less the same time—in the 1960s—and with this there has been much dissatisfaction and criticism of physicians and the medical profession. There have been many interventions and intrusions by both government and the private sector into medical practice and health care delivery. Many of the actions taken have bordered on the punitive. Virtually all have been stressful.

How have physicians and the medical profession been responding to 20 years or more of this stress? At first there were dismay, incomprehension and hostile reactions toward all the real and perceived third party "intrusions"; to a greater or lesser extent these responses persist. But there has been a gradual realization that health care is now a new ball game and, further, that the rules of this new game have yet to be fully determined. No one really seems to know what to do. There are many unresolved questions—compensation, ethics and turf, for example. Government intervention to try to control costs has been largely at the expense of the poor, the elderly and, yes, physicians. Relatively unfettered economic competition in health care is lately being tried in the private sector, but so far it has not come up to the expectations of those who advocated this approach.

One may be genuinely heartened, however, by the way individual physicians and the profession as a whole seem to be responding. It is as though they are going back to their roots, to the reasons why most entered the profession in the first place and are now drawing strength and even power from returning to this original commitment. Most applicants to medical school, both yesterday and today, seem to choose medicine because they are fascinated by the new biomedical science, care about people, want to help those who need help and want to do something with their lives for the good of humanity. In these stressful times we begin to see new emphasis being given to the caring function of a physician within the practice of modern scientific medicine. We see patients receiving much the same quality of care, whatever the payment mechanism, and there is growing evidence that substantial amounts of care are actually being given freely or at reduced cost to patients who cannot pay. We see physicians reaching out to acquire all kinds of new skills that they need in order to play in the new ball game that health care is so obviously becoming.

But it is not only individual physicians who seem to be returning to their roots. The profession itself seems also to have begun to draw strength from the very reasons its member physicians entered medicine in the first place. The profession continues to promote biomedical science and human caring in research, education and medical practice, and this enables it to speak from a position of authority in the public arenas of health care. The organized profession has begun to speak out with authority on behalf of the sick and afflicted who really have no other organized advocate in a ball game that seems to be increasingly dominated by third party special interests. In another dimension, organized medicine has begun to take what might be called affirmative action in the new environment of health care. The AMA House of Delegates has spoken out authoritatively on AIDS. It has endorsed a monumental collaborative study resulting in a proposed health policy agenda for the American people, and it has developed a thoughtful proposal for realistically refinancing the Medicare program. In the legislative arena the profession is developing formidable skills that are enabling it to help shape the new health care ball game and to lead the way toward solving problems such as tort reform that seem somehow to surface first in health care, only later to reach out to affect the general society.

It should never be forgotten that the medical profession has great inherent strengths. It is composed of motivated, self-disciplined, intelligent men and women who have an intimate knowledge of human biology, human nature and the human condition. Physicians permeate every aspect of society. One senses that the current stress, far from resulting in the demise of a noble profession, rather, will lead to a resurgence of a noble profession's authority and power as it returns to its individual and collective roots and then begins to identify, develop and use the new tools and new skills that are needed for it to serve well in the changing environment of health care. As long as we remember where we are coming from as physicians, we can all stand tall!

MSMW

The Treatment of Obstructive Sleep Apnea—Who, When, How?

DURING THE PAST DECADE, the obstructive sleep apnea syndrome has become widely recognized as a disorder of major clinical importance.[1,2] This importance arises from three considerations: the disorder is extremely common, with an estimated prevalence of 1% to 3% in the adult male population[3]; it is the leading cause of excessive daytime sleepiness,[4] and it may result in the development of pulmonary hypertension, right ventricular failure, chronic carbon dioxide retention, nocturnal cardiac arrhythmias and possibly sudden death during sleep.[5] In addition, an association with systemic hypertension and strokes has also been claimed.[6,7] As an appreciation of the clinical importance of obstructive sleep apnea has become more widespread among physicians and the public, a sense of urgency has developed in initiating treatment of the disorder. This sense of urgency is based on the assumption that, if left untreated, the syndrome will become progressively more severe and lead to a serious or even fatal outcome, either as a result of the patient falling asleep inap-

propriately or due to the cardiopulmonary sequelae of the disorder.

Given these considerations, it is not surprising that a multitude of treatments has been proposed for the obstructive sleep apnea syndrome. The many therapeutic approaches that have been advocated in recent years are reviewed in detail by Wiggins and Schmidt-Nowara in this issue of the JOURNAL. Several important points emerge from this review. First, the efficacy of most of the current proposed treatments remains controversial because, with few exceptions,[8,9] the treatments have not been subjected to rigorous clinical trials. The need for prospective controlled studies in this field became clear at a recent workshop on respiratory disorders of sleep sponsored by the National Institutes of Health (NIH) and may result in NIH-sponsored multicenter trials of the treatment of obstructive sleep apnea.[10]

In the absence of appropriate therapeutic studies to provide direction, how should physicians manage their patients who have this disorder? One approach is outlined in the current review by Wiggins and Schmidt-Nowara. In our center, we follow a somewhat similar but even more conservative approach. Patients with obstructive sleep apnea of mild to moderate severity are advised to lose weight, avoid using alcohol and sedative medications, maintain nasal patency and avoid sleep in the supine posture. In some patients these measures are extremely effective. Those with moderate to severe obstructive sleep apnea may be given a trial of protriptyline hydrochloride[8] in addition to the preceding management, but the majority are treated with nasal continuous positive airway pressure (CPAP),[11] which is successful in at least 75% of patients. The advantage of both protriptyline and nasal CPAP is that their use can be withdrawn if no benefit follows or if side effects develop. In contrast, uvulopalatopharyngoplasty and other surgical treatments (apart from tracheostomy) are of long-term benefit in no more than 50% of unselected patients[10] and are irreversible. For these reasons we do not advocate such procedures at the present time, but rather await the results of properly conducted clinical trials of their efficacy.

In addition to the question of *how* obstructive sleep apnea should be treated, an even more fundamental issue is that of *whom* to treat and *when* to treat them. These questions have gained increased prominence during the past two to three years as doubts have begun to emerge about the assumptions on which the need for treatment has been based. The sense of urgency to treat all patients who have obstructive sleep apnea, referred to above, probably arose because the disorder was initially identified in patients with the pickwickian syndrome of obesity, excessive daytime sleepiness and cardiorespiratory failure.[12,13] It was also shown that relief of the disorder in pickwickian patients by a tracheostomy ameliorated most of its clinical features, including daytime sleepiness and cardiorespiratory failure.[14] Thus, a firm link was established between obstructive sleep apnea and the pickwickian syndrome; and, not surprisingly, the notion developed that, if left untreated, obstructive sleep apnea would lead to severe daytime somnolence and eventually chronic cardiorespiratory failure. Considerable clinical experience now suggests that this is not the case, however. Indeed, based on cross-sectional studies, it appears the serious cardiorespiratory complications develop in only, at the most, 10% to 15% of patients.[15] Furthermore, although it has been assumed that patients with only a few obstructive events during sleep will have more such events with the passage of time, this assumption also remains to be established. Thus, there is uncertainty as to when to intervene in the course of the disorder.

The dilemma of knowing which patients to treat and when to treat them is exemplified in the current review by Wiggins and Schmidt-Nowara. On the one hand, they point out that polysomnography is the current standard for objectively defining the problem in all its dimensions; but, on the other hand, pathologic sleepiness, the principal consequence of the obstructive sleep apnea syndrome, is used to classify the severity of the disease. Although there is little serious doubt that patients with severe daytime sleepiness require treatment of some type, regardless of the severity of polysomnographic abnormalities, the converse is not true. For example, we have identified patients whose polysomnographic studies indicate a moderate to severe sleep apnea disorder, but who do not have an obstructive sleep apnea syndrome in that they lack the important clinical features of the disease, including daytime sleepiness, restless nocturnal sleep, morning headache, intellectual deterioration or personality changes. Should such patients be treated to prevent the emergence of clinical symptoms or the development of cardiorespiratory complications? What about patients who simply snore on a regular basis but who have no apneas or hypopneas during sleep? Should they be treated prophylactically to prevent the development of obstructive sleep apnea? Unfortunately, these and many related questions cannot be answered at the present time because the natural history of these various forms of breathing disturbance during sleep is unknown. Indeed, the uncertainties regarding the clinical course of the disorder have led to the conclusion that "there is an urgent need for prospective studies of the natural history of the sleep apnea syndromes,"[10] support for which is also under consideration by the NIH. Such studies will of necessity take several years to complete. In the meantime, physicians will have to rely on their clinical judgment and the published studies that are available to decide when and how to treat obstructive sleep apnea, bearing in mind that definitive answers to both of these questions remain to be established.

During the past ten years, great strides have been made in understanding the pathogenesis and the pathophysiology of the obstructive sleep apnea syndrome. The major challenges for the next decade are to define the natural history of both subclinical and clinical forms of the condition and to establish the efficacy of several treatment modalities. Both of these challenges can be met by the combined efforts of the respiratory and sleep scientific communities.

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Of Epidemics and Politicians

THE RECENT POLITICIZATION of the AIDS epidemic is a phenomenon that probably could not have been avoided for at least two reasons. First, when politicians in legislatures are confronted with a new problem, they usually look back to see how comparable problems have been handled in the past. Second, it is difficult, if not well nigh impossible, for them to provide genuine leadership in finding creative solutions for new and complex problems, especially if those problems are unprecedented. The leadership, if any, must come from outside the political arena, unless perchance it can be found among the young, bright, innovative and often well-paid executive assistants to the elected or appointed officials. Contrary to a general assumption, politicians more often follow than lead. Behaving as might be expected, therefore, they are addressing the current AIDS epidemic as if it were like other earlier epidemics of infectious diseases, and we hear cries for compulsory testing, segregation of prisoners and even quarantine of those who are or may be ill with the disease. Already becoming highly politicized, it is more than likely that the AIDS epidemic will become an important issue in the coming elections.

As noted above, if politicians are to deal creatively or even effectively with such a new kind of problem, knowledgeable leadership must come from somewhere, and preferably from persons or groups who have some understanding of the problem and training in how to deal with it. If, as is so often the case, this does not happen, the politicians will then somehow manage to fill the vacuum of leadership themselves, usually by responding to their own personal beliefs or possibly those of their constituents. The result is that the need and the power to act falls into the unguided hands of those who have power and responsibility but no real understanding of what to do.

AIDS or any epidemic of infectious disease is clearly a medical and public health problem. It is well known that the political process can be influenced by individuals or groups that are proponents of legislative action of various kinds. The medical profession has substantial skills and resources for doing just this. Ought not organized medicine and the medical profession as a whole be as visible in promoting appropriate specific legislation for control of the AIDS epidemic as it now is in promoting legislation on behalf of its own professional interests and those of its patients? For many reasons one might think so. Where else should the politicians be looking for informed leadership and guidance?

MSMW

Case Reports

Traumatic Hypopituitarism Due to a Gunshot Wound

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PANHYPOPITUITARISM DUE TO a gunshot wound to the head has been described only once previously.[1] We report the case of a 12½-year-old boy who was shot in the left temporal region, with the bullet lodging in his sella turcica. The striking radiographic evidence of pituitary ablation produced by this injury was confirmed by studies of his pituitary function. For these studies, we used pharmacologic agents that stimulate pituitary secretion indirectly through the hypothalamus and releasing factors that act directly on the pituitary. Comparing results from these two methods of study can be helpful in defining hypopituitarism as due to either pituitary or hypothalamic deficiency.

Report of a Case

At 12 years 6 months of age, the patient sustained a gunshot wound to his head. Until the injury he had been healthy, and his height was reportedly above average for age. He was prepubertal at the time of the injury. Skull radiographs done after the injury showed that the bullet had lodged in the sella turcica (Figure 1). Initial arteriograms showed no gross vascular abnormality (Figure 2).

He initially responded well to medical management, and a decision was made that surgical removal of the bullet would be more dangerous than leaving it undisturbed. During a three-week hospital stay at another institution, clinical observation and a modified water-deprivation test showed that he had diabetes insipidus. A serum thyroxine (T_4) concentration was 2.7 μg per dl and an 8 AM cortisol level was 10 μg per dl. Following an overnight challenge with metyrapone given orally, his plasma 11-desoxycortisol concentration showed an insignificant increase from 0.1 to 0.3 μg per dl. With this evidence of pituitary insufficiency, replacement therapy with desmopressin acetate (DDAVP), levothyroxine sodium and hydrocortisone was initiated.

Six months after his injury severe headaches developed and he was found to have an enlarging intracranial aneurysm. This was treated by surgical ligation of the left carotid artery. He also failed to grow after the gunshot injury. In the 16-

(Trujillo-Juarez D, Culler FL, Ganelin RS, et al: Traumatic hypopituitarism due to a gunshot wound. West J Med 1987 Nov; 147:591-593)

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
GHRH = growth hormone-releasing hormone
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
T_4 = thyroxine
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone
UCSD = University of California, San Diego

Figure 1.—A lateral skull radiograph shows the presence of a bullet within the sella turcica. An anteroposterior view confirming the location of the bullet is not shown.

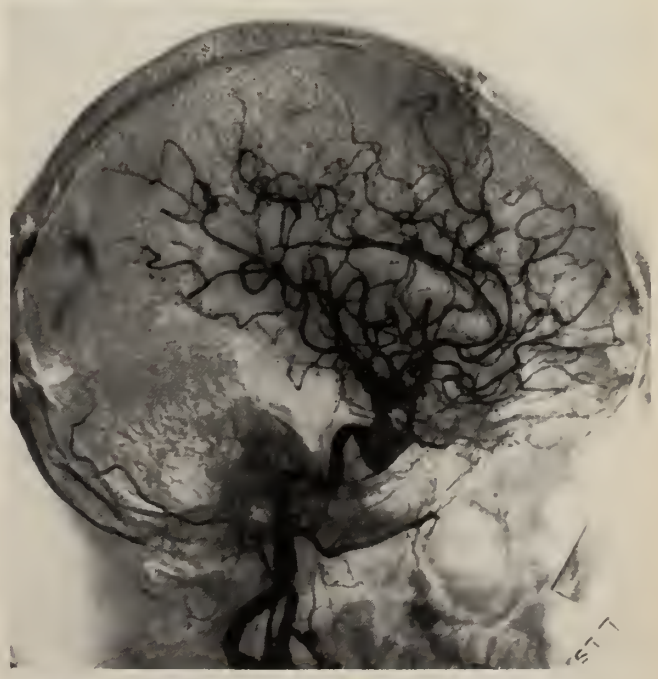

Figure 2.—An arteriogram done immediately after the wound was sustained shows no vascular abnormality.

TABLE 1.—*Pituitary Hormone Concentrations at Base Line and Following Provocative Stimulation Testing*

Hormone	Arginine		GHRH		TRH		GnRH-1		GnRH-2	
	Basal	Peak	Basal	Peak	Basal	Peak	Basal	Peak	Basal	Peak
Growth hormone, ng/ml	2.6	2.6	2.1	2.5	...	...	...	...	...	...
Prolactin, ng/ml	0.8	1.0	...	...	1.0	1.6	...	...	...	...
TSH, μU/ml	...	...	...	...	2.6	2.9	...	...	...	...
LH, mIU/ml	...	...	...	...	...	...	3.0	4.1	3.8	3.5
FSH, mIU/ml	...	...	...	...	...	...	2.0	2.4	2.0	2.3

FSH = follicle-stimulating hormone, GHRH = growth hormone-releasing hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone, TSH = thyroid-stimulating hormone

month interval after the wound he grew only 6 mm (¼ in), and growth hormone deficiency was suspected. He was then referred to the University of California, San Diego (UCSD), Medical Center for further evaluation and treatment.

At the time of this initial evaluation, he was 13 years 11 months old and was using desmopressin intranasally and taking thyroxine and hydrocortisone replacement. On physical examination he appeared thin, prepubertal, with a height of 147 cm (58 in)—3rd percentile—and a weight of 43.9 kg (97 lb)—15th percentile. His pulse rate was 80 per minute and his blood pressure 105/70 mm of mercury. There was a 3- by 3-cm scar in the left temporo-occipital region. Results of the examination of his head, eyes, ears, nose and throat were otherwise normal. The thyroid gland was not palpable. Other pertinent findings included a prepubertal phallus, testes that were 2 cm in maximum diameter and no pubic or axillary hair. The neurologic examination showed no abnormalities.

Initial laboratory studies elicited the following values: a bone age of 11 years 6 months, prolactin 2.1 ng per ml, luteinizing hormone (LH) 3.0 mIU per ml, follicle-stimulating hormone (FSH) 2.0 mIU per ml, thyroid-stimulating hormone (TSH) 2.9 μU per ml and T_4 8.9 μg per dl. The patient was then studied using protocols designed to evaluate hypothalamic and pituitary function. These protocols were approved by the UCSD Institutional Committee on Investigations and Activities Involving Human Subjects, and informed consent was obtained. Studies were done in the Clinical Research Center at the UCSD Medical Center following an overnight fast.

Drugs were administered and blood specimens obtained through indwelling intravenous catheters. The synthetic replicates of growth hormone-releasing hormone (GHRH)[2] and gonadotropin-releasing hormone (GnRH)[3] were generously supplied by Nicholas Ling, MD, and Roger Guillemin, MD, of the Salk Institute, La Jolla, California. Radioimmunoassays for growth hormone, LH, FSH, prolactin and TSH were done as previously described.[4] For the prolactin assay standard NPA batch #5 AFP 1528C was used.

The patient was first given arginine-hydrochloride, 0.5 grams per kg, intravenously over 30 minutes.[5] Blood specimens were taken to measure growth hormone and prolactin levels at baseline and every 15 minutes for an hour. He was then given two bolus injections of 10 μg of GnRH intravenously, each separated by two hours.[6] Blood specimens were taken at 15-minute intervals for two hours after each injection, and concentrations of LH and FSH were measured. A 200-μg bolus infusion of thyrotropin-releasing hormone (TRH) was given with the second GnRH injection, and TSH and prolactin levels were measured in the specimens collected over the last two hours.[4] Finally he was given GHRH, 1 μg per kg, as a bolus intravenous infusion.[7] Blood specimens to measure growth hormone levels were collected at base line and 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes after administering GHRH. Results of all studies are shown in Table 1.

Discussion

This report provides graphic evidence of the consequences of traumatic hypopituitarism, in this case due to a bullet injury to the pituitary gland. The patient's hypothalamic-pituitary function test results are consistent with the radiographic evidence of a primary pituitary injury. He had low baseline concentrations of all pituitary hormones and showed no significant increase in the serum concentration of any of these hormones following direct pituitary stimulation with the hypothalamic-releasing hormones TRH, GnRH and GHRH. In cases such as this, in which primary pituitary insufficiency is documented, a concomitant hypothalamic injury cannot be excluded. Testing will identify a hypothalamic defect only if pituitary function remains intact. When patients with a specific hypothalamic injury are tested, they usually have absent growth hormone responses to arginine, insulin and levodopa (stimuli that act on the hypothalamus); they often show elevated basal and stimulated prolactin concentrations,[8,9] and they frequently show blunted but measurable pituitary hormone responses following direct pituitary stimulation with hypothalamic-releasing hormones.[10,11]

A similar case of gunshot-induced hypopituitarism in a 32-year-old man has been described previously.[1] This patient also had radiographic evidence of a bullet lodged in the sella turcica, deficient release of pituitary hormones and minimal neurologic sequelae. He did not have diabetes insipidus and did show a measurable but small response of serum luteinizing hormone after stimulation with gonadotropin-releasing hormone. These findings suggest that this man probably had residual hypothalamic and posterior pituitary capability for release of the antidiuretic hormone and some degree of persisting anterior pituitary secretion. Our patient, however, had diabetes insipidus and showed no increase in serum concentrations of pituitary hormones following provocative testing, suggesting that pituitary destruction was complete.

The accident that befell this boy provided a unique opportunity to relate radiographic and endocrine findings in a person with apparent pituitary injury. Rarely is it possible to anatomically define so precisely the site of an injury and study its functional consequences. The availability of synthetic replicates of hypothalamic-releasing factors that permitted this study should lead to more precise definition of the sites of hypothalamic-pituitary injury.

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Hypernatremia Associated with Cathartics in Overdose Management

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ACTIVATED CHARCOAL has held a recognized role in acute poisoning management for more than 150 years.[1,2] Its remarkable capacity to absorb chemicals has led to wide acceptance for the initial gastrointestinal decontamination.[1] Recent reports using multiple doses have shown increased systemic clearance for several drugs including phenobarbital,[3] theophylline,[4] digitoxin,[5] carbamazepine[6] and phenylbutazone.[6] Multiple doses of activated charcoal also have been recommended for toxic ingestions of drugs that undergo enterohepatic circulation or gastric secretion (tricyclic antidepressants and phencyclidine).[7] Although activated charcoal avidly absorbs toxins, binding is not irreversible.[1] Cathartic administration has therefore been recommended to hasten the elimination of the charcoal-toxin complex from the bowel and to prevent toxin desorption.[8] The use of cathartics has also been advocated for preventing charcoal impaction when used in multiple doses.[3,9]

Despite the wide use of cathartics, clear evidence of risk and benefit has not been described.[1] POISINDEX, a commonly used resource for poison management,[7] recommends for phencyclidine overdose that several doses of activated charcoal be administered every two to six hours with a cathartic until charcoal appears in the stool. A particular cathartic is not preferred but several precautions are mentioned:

- Doses should not be repeated if bowel sounds are absent.
- The fluid and electrolyte status should be monitored in a health care facility, especially in children.
- The safety of the repeated use of cathartics has not been established when used with multiple-dose charcoal regimens.
- In young children, cathartics should be administered no more than one to two times per day.

In a recent editorial on the rebirth of activated charcoal, Spyker said,

> Although some cathartic is probably necessary to prevent formation of intestinal charcoal briquettes, we need to further assess quantitative importance of sorbitol and other cathartics. We must also assess the adverse effects of the cathartic on diarrhea and fluid and electrolyte management.[10]

Minocha and co-workers, after investigating the effects of single doses of 150 ml of 70% sorbitol, concluded that the possible effects of multiple-dose regimens and the effects in pediatric and geriatric populations need further study.[11] Case reports of hypernatremia associated with using cathartics are not found in the medical literature. Thus, the risks and benefits of multidose charcoal-cathartic combinations are inadequately defined.

We report three cases of severe hypernatremia associated with three different multidose charcoal-cathartic regimens during treatment of acute intoxication.

Reports of Cases

Case 1

The patient, a 22-year-old woman, was admitted to the emergency department with a presumptive overdose of amitriptyline and naproxen. She was initially lethargic but shortly became comatose. Her temperature was 37.2°C (99°F), pulse 108 per minute, respirations 26 per minute and blood pressure 120/70 mm of mercury. Her pupils were 4 mm, equal, round and sluggishly reactive to light. The abdomen was soft, bowel sounds were normally active and the skin was warm and dry. The results of the physical examination otherwise were normal. The electrocardiogram (ECG) showed a sinus rhythm with a PR interval of 0.20 seconds, a QRS duration of 0.12 seconds and a QT interval of 0.36 seconds. A chest x-ray film, leukocyte count and differential, hemoglobin and hematocrit were all normal. A blood alcohol level was 79 mg per dl. An endotracheal tube was inserted and gastric lavage done without return of pill fragments. She was then treated with a regimen of fluids given intravenously, 40% oxygen and 50 grams activated charcoal and 300 ml of a magnesium citrate solution (Citroma, National Magnesia Company, Glendale, NY) every four hours by nasogastric tube (Figure 1). A preparation of activated charcoal in a 70% sorbitol solution (Actidose charcoal solution, Paddock Laboratories, Inc, Minneapolis) was inadvertently administered. The initial serum sodium level two hours after admission was 138 mmol per liter. A solution of 5% dextrose and 0.45% saline was being administered at 75 ml per hour and the urine output was 150 ml per hour (Figure 1). Fluid administration 15 hours after admission was increased due to a decreasing urine output. The urine specific gravity had increased to 1.030. After 27 hours, the serum sodium concentration was

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noted to be 160 mmol per liter. Repeat determinations confirmed the presence of hypernatremia. The serum urea nitrogen level increased from 6.0 mg per dl on admission to 11 mg per dl, and the serum creatine level increased from 0.7 mg per dl to 1.3 mg per dl. The patient was still stuporous and large, watery, charcoal stools were noted. Fluid administration was increased again and changed to a 5% dextrose solution given intravenously and additional tap water through a nasogastric tube. The serum sodium level rose to 170 mmol per liter 34 hours after admission and then gradually declined with continued water replacement. Urine output, urine specific gravity and the serum sodium level had returned to normal 50 hours after admission. The patient was alert, oriented and taking oral feedings without diarrhea.

Case 2

The patient, a 34-year-old paraplegic woman, was admitted to the emergency department with an amitriptyline and barbiturate overdose. On admission she was combative but soon became lethargic and then comatose, requiring endotracheal intubation for respiratory support. Her pulse was 120 per minute and pupils were 3 mm and reactive to light, but sluggish to respond. The abdomen was flat with hypoactive bowel sounds, and deep tendon reflexes were equal with bilateral Babinski's reflexes. The results of the physical examination were otherwise normal.

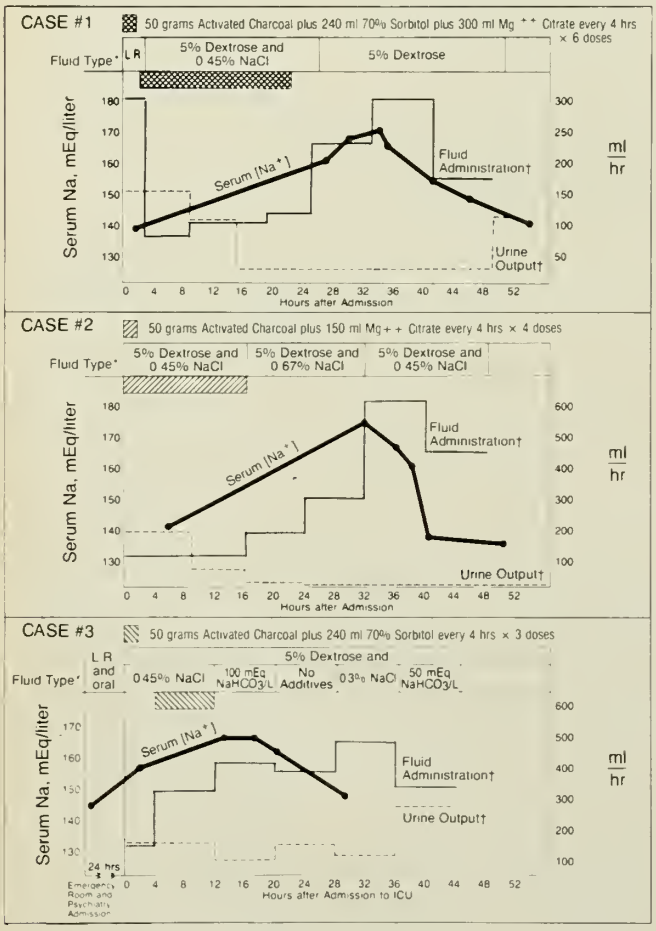

Figure 1.—The graph shows rising serum sodium concentrations accompanied by declining urine outputs despite the administration of fluids in excess of maintenance requirements in three patients who were administered multiple doses of cathartics and charcoal during overdose management.

*Most representative fluid type per time interval.
†Average ml/hr/6- to 8-hr time interval.
—•— = serum [Na+], ····· = fluid administration, --- = urine output, ICU = intensive care unit, L.R. = lactated Ringer's solution

The ECG showed a heart rate of 150 per minute, a PR interval of 0.14 seconds, a QRS duration of 0.06 seconds, a QT interval of 0.28 seconds and peaked P waves. The hemoglobin was 10 grams per dl (100 grams per liter), the hematocrit was 31.3% (0.313) and the leukocyte count was 12,500 per μl with a normal differential. Urinalysis showed a specific gravity of 1.010, 4+ protein, 50 to 100 leukocytes per high power field and 4+ bacteria. A urine Gram's stain showed 0 to 3 leukocytes, 5 to 10 gram-negative rods and 0 to 3 gram-positive cocci per oil immersion field. A chest x-ray film and results of a lumbar puncture were normal.

A gastric lavage was done, which did not yield evidence of pill fragments. Therapy was initiated with intravenous administration of fluids, nafcillin sodium and tobramycin given intravenously and 50 grams of activated charcoal and 150 ml of magnesium citrate every four hours through a nasogastric tube. The initial serum sodium level was 138 mmol per liter and a blood glucose level was 140 mg per dl (7.7 mmol per liter). A solution of 5% dextrose and 0.45% saline at 100 ml per hour was administered and the urine output was more than 180 ml per hour (Figure 1). Urine output 14 hours after admission decreased to less than 20 ml per hour with a urine specific gravity of 1.030. Her temperature was 40°C (104°F), respirations were 47 per minute and the blood pressure was 90/64 mm of mercury. The nursing staff noted black liquid stools too numerous to count. The patient removed the endotracheal tube herself nine hours after admission and was alert and oriented to person and place but not to time. Volume expansion with a normal saline solution was attempted, and the volume of maintenance fluids was increased to 300 ml per hour. Her serum sodium level 32 hours after admission was 164 mmol per liter—corrected to 175 mmol per liter due to hyperglycemia—and a blood glucose level was 698 mg per dl. The serum urea nitrogen concentration was increased to 27 and serum creatine to 2.9 mg per dl from initial values of 12 and 0.6 mg per dl, respectively. An insulin infusion was begun and intravenous fluids were changed to a solution of 0.45% sodium chloride.

Her serum sodium level 48 hours after admission had returned to normal, but urine output remained low and the patient continued to deteriorate clinically. A generalized paralytic ileus occurred 20 hours after admission and continued, accompanied by massive abdominal distention, rising ventilation pressures, mottling of the lower extremities and hypotension despite supportive measures. The patient died 58 hours after admission.

The autopsy showed massive thrombosis of the portal vein and a small bowel ileus. Gastric analysis showed acetaminophen, amitriptyline and an unidentified substance. A urine toxicology screen was positive for acetaminophen, amitriptyline and nortriptyline. A postmortem blood amitriptyline concentration was 1,151 ng per ml.

Case 3

The patient, a 37-year-old man, was found unresponsive by his brother. According to his friends, he had been drinking alcohol excessively and smoking phencyclidine (PCP). In the emergency department, he was obtunded, responsive to pain and occasionally combative. Superficial abrasions and contusions were noted on all four extremities. Except for nys-

tagmus, the results of the physical examination were normal. He was treated with nasogastric intubation, gastric lavage and administration of 50 grams activated charcoal, 300 ml magnesium citrate solution and a lactated Ringer's solution given intravenously. A urine drug screen was positive for phencyclidine and nicotine. Arterial blood gas measurements, serum electrolytes, blood levels of glucose, urea nitrogen and alcohol, an ECG, urinalysis and cranial computed tomography were all normal.

During the eight-hour emergency department stay, he received 1,800 ml of fluid, 10 mg diazepam and 10 mg haloperidol given intramuscularly for agitation. His mental state improved significantly and he was admitted to the psychiatric ward. There he became increasingly disoriented, intermittently lethargic, febrile to 39°C (102°F) and was therefore transferred to the intensive care unit 20 hours after the initial emergency department presentation.

Due to phencyclidine intoxication and evidence of injury (multiple abrasions), rhabdomyolysis was considered. Extracellular volume expansion with a solution of 5% dextrose and 0.45% sodium chloride was initiated. A creatine kinase value of 46,000 units per liter confirmed muscle damage. Activated charcoal, 50 grams in 240 ml of 70% sorbitol (Actidose), was given through a nasogastric tube every four hours. Thirteen hours after medical transfer and two hours after his third dose of charcoal-sorbitol, his serum sodium concentration had increased to 165 mmol per liter, urine output had decreased to 50 ml per hour and a urine specific gravity was 1.029 (Figure 1). His blood pressure decreased from 130/65 mm of mercury (when admitted to the intensive care unit) to 110/50 mm of mercury, and urine electrolyte determinations showed a sodium of 29 and a potassium of 45 mmol per liter. During the previous eight hours, nurses had noticed several large and loose charcoal bowel movements. Water replacement with intravenous fluids returned the sodium concentrations to normal ranges over the next 20 hours, accompanied by increasing urine output and a decreasing urine specific gravity (Figure 1). The patient's mental state improved. After a seven-day stay on the medical floor, he was transferred back to the psychiatric unit because of bizarre behavior and suicidal ideas.

Discussion

Hypernatremia in adults is generally a chronic process associated with other illnesses that limit fluid intake—such as an elderly patient with a cerebrovascular accident. Acute hypernatremia has most commonly occurred due to solute loading—saline abortion, the use of sodium chloride as an emetic, malfunctioning hemodialysis or peritoneal dialysis equipment or sodium bicarbonate administration during a cardiac arrest.[12]

In each of the cases presented, the history and clinical evidence exclude the commonly recognized causes. Dilute sodium-containing fluids were administered at normal maintenance or replacement rates of infusion. Urinary water losses indicated appropriate volumes and specific gravities for the clinical volume states present. In case 2, fever and tachypnea may have exaggerated losses of water from the skin and respiratory tract but are unlikely to account for the entire deficit, considering a controlled environment and humidified air. Osmotic diuresis from hyperglycemia is also unlikely as the initial blood glucose level was 140 mg per dl and urine output remained low. Acute colonic water loss due to the osmotic or saline cathartics administered remains the most likely cause of acute hypernatremia. In all three cases, nursing notes specifically document excessively loose and watery stools. In case 2, stools were occurring in frequencies too numerous to count. In case 1, the patient inadvertently received six doses of Actidose (a solution of 50 grams activated charcoal in 240 ml of 70% sorbitol) plus 300 ml of magnesium citrate solution over a period of 24 hours. The sorbitol vehicle was not specified on the front label of the Actidose preparation. Sorbitol is classified as a pharmaceutical aide[13] and an inactive ingredient[14] by the Food and Drug Administration.

Sorbitol is a hexahydric alcohol that is primarily used as a sweetener in diabetic diets and some low-calorie beverages. It has been used medicinally as a laxative and to facilitate the passage of sodium polystyrene sulfonate (Kayexalate) through the intestinal tract. The addition of 70% sorbitol as a vehicle for activated charcoal overcomes its grittiness, improves palatability, maintains particles in suspension for prolonged periods of time and provides a cathartic action.[8]

Several authors identify possible fluid and electrolyte losses due to the use of sorbitol. Diarrhea and electrolyte changes have been noted in children taking a vitamin C preparation containing sorbitol.[2] Minocha and associates studied the effects of a single dose of 30 grams of activated charcoal in 150 ml of 70% sorbitol on serum osmolarity, electrolytes, metabolic profile, magnesium level, hepatic enzymes and complete blood count in healthy adults.[11] They noted only small changes in serum sodium and phosphorus concentrations four hours after drinking the charcoal-sorbitol mixture, but recommended that the possible effects of multiple-dose regimens and the effects in pediatric and geriatric populations required further study. Krenzelok and colleagues in a single-dose study in volunteers examined the gastrointestinal transit times following three separately administered cathartics combined with 50 grams of activated charcoal—130 grams of 70% sorbitol, 300 ml of magnesium citrate solution and 30 ml of 50% magnesium sulfate.[15] Sorbitol was clearly the most rapidly acting cathartic, producing a charcoal-colored stool in a mean time of 1.6 hours compared with 4.2 hours for magnesium citrate and 9.3 hours for magnesium sulfate. In the sorbitol group, some patients reported a frequency of 10 to 15 watery stools and complained of more abdominal cramping before catharsis. The authors warned that physicians should be aware of the potential for fluid and electrolyte depletion if sorbitol is used with each dose of activated charcoal in a multidose regimen.

Despite the demonstrated potency of sorbitol in these doses, its pharmaceutic classification allows commercial products to be sold over the counter without package insert information.

The outcome in two of our cases was uneventful following the correction of water losses. As described in case 2, however, the patient died of complications of the overdose and supportive management.

Conclusions

The safety and efficacy of repeated cathartic administration have not been established. Overdosed patients who may have ingested several drugs affecting bowel function may be at risk for rapid shifts of water and electrolytes into the bowel due to multiple doses of saline or osmotic cathartics. We recommend that administration of such cathartics should be limited to one or two doses per 24-hour period in children and

adults until further study defines the risks and benefits of this practice. We also suggest reconsideration of labeling guidelines for sorbitol-containing products formulated for pharmacologic effects.

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Rhabdomyosarcoma of the Heart with Cerebral Metastases

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RHABDOMYOSARCOMA OF THE HEART is a malignant neoplasm composed of cells that display features of striated muscle. This tumor is rare and accounts for less than 5% of all tumors and cysts of the heart and pericardium.[1] Cardiac rhabdomyosarcomas may occur in any of the four chambers of the heart, but a portion of the tumor always involves the myocardium, even when the intracavitary component predominates.[1] The clinical findings are determined by the anatomic location of the tumor and the degree of intracavitary obstruction.[2] The presenting features include congestive heart failure, precordial pain, pericardial effusion, conduction abnormalities, obstruction of the vena cava and sudden death.[2] Surgical treatment is usually not effective against cardiac rhabdomyosarcomas because of the extent of myocardial involvement or the presence of metastases. Because the tumor is rare, most reports consist of a single case or only a few cases and, thus, there are limited descriptions of the sites of metastases from this tumor.

A computer-assisted literature search elicited only one case[3] of cerebral metastases from cardiac rhabdomyosarcoma. In this report I describe the second case of cerebral involvement by this unusual neoplasm and the first case reported in the English language literature.

(Geyer SJ: Rhabdomyosarcoma of the heart with cerebral metastases. West J Med 1987 Nov; 147:596-597)

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Report of a Case

The patient, a 23-year-old man, had the sudden development of a cough productive of brown sputum. He had a systolic murmur and a pericardial friction rub. On radiographic examination there were bilateral pulmonary infiltrates, and a diagnosis of *Mycoplasma pneumoniae* was made. He did well, with resolution of the pneumonia, but one month later pulmonary edema developed. He had a high-pitched, heaving systolic and diastolic murmur.

A chest radiograph showed increased size of the left atrium, and an electrocardiogram revealed sinus tachycardia with nonspecific ST-T changes. An echocardiogram showed a mass in the left atrium, and cardiac catheterization revealed that the mass in the left atrium extended through the mitral valve. The patient underwent right and left atriotomies and atrioseptostomy for resection of the tumor. The tumor arose from the posterior wall of the left atrium. The surgical specimen showed rhabdomyosarcoma, and the margins of the specimen were free of tumor. The resected tumor was 10 by 8 by 6 cm and had a firm, white, fleshy appearance with areas of hemorrhage and necrosis. On microscopic examination of the primary tumor there was a neoplastic proliferation of cells with abundant eosinophilic cytoplasm and large, hyperchromatic nuclei displaying numerous mitoses. Cross-striations characteristic of skeletal muscle differentiation were found in the tumor cells (Figure 1).

The patient did well postoperatively, was evaluated for metastases and found to be free of tumor. He received chemotherapy consisting of cyclophosphamide (Cytoxan), 200 mg, and vincristine sulfate, 2 mg, intravenously per week for 12 weeks and dactinomycin, 0.5 grams, intravenously for 5 days every 3 months. After the 11th postoperative week, the vincristine therapy was discontinued because of tingling in the patient's hands. He received the other chemotherapy without apparent toxicity.

Six months later the patient had throbbing pain in the left pectoral region, shoulder and upper arms. He was admitted to hospital where a workup included a bone scan and multigate analysis (MUGA) scans, which were normal. He continued to

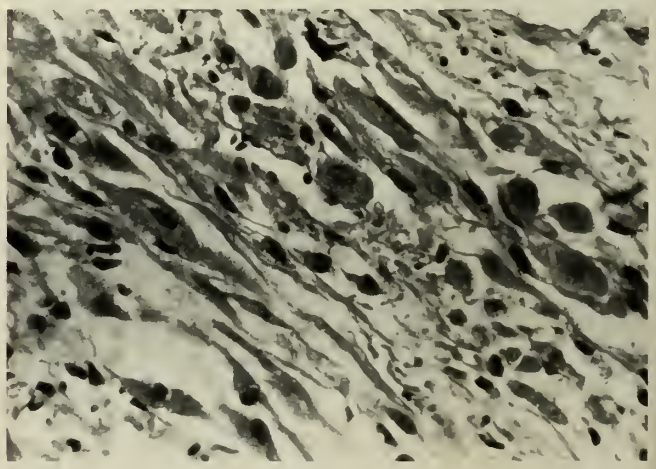

Figure 1.—Tumor cells from the occipital mass contain cross-striations, which identify the tumor as a rhabdomyosarcoma (Hand E, original magnification × 450).

receive chemotherapy and was diagnosed as having the shoulder-hand syndrome. On the third day of hospital stay the patient complained of bumping into objects on his right side and had had loss of vision in the right visual field. The results of a neurologic evaluation were unremarkable except for the loss of vision, and arrangements were made for formal visual field examinations as an outpatient. The patient was discharged to be followed in the outpatient oncology clinic and to continue to receive chemotherapy.

The patient was readmitted two months later when he complained of bifrontal headaches and was noted to have a right temporal field cut. On physical examination on readmission, he had mild anomic aphasia, right hemiparesis and right homonymous hemianopia. He also had bilateral papilledema. A computed tomographic scan showed a hypervascular enhancing mass in the left occipital region with an associated transfalcial shift and trapped left temporal horn (Figure 2). Because it was felt this could be a metastatic mass, the patient was given antiedema agents and anticonvulsant medications. A neurosurgical consultant thought there were several lesions on the scan and that surgical procedures would be of no benefit. The patient had a steady downhill course and, despite continued treatment with antiedema agents and radiation therapy, he became comatose and died a month after readmission. The autopsy examination revealed metastatic rhabdomyosarcoma in the left parieto-occipital lobe with associated severe cerebral edema. There was hemorrhagic necrosis of the central white matter in the left occipital lobe. Tumor also was present in the soft tissue near the aortic arch, in the mesenteric fat as a solitary lesion and in the bone marrow.

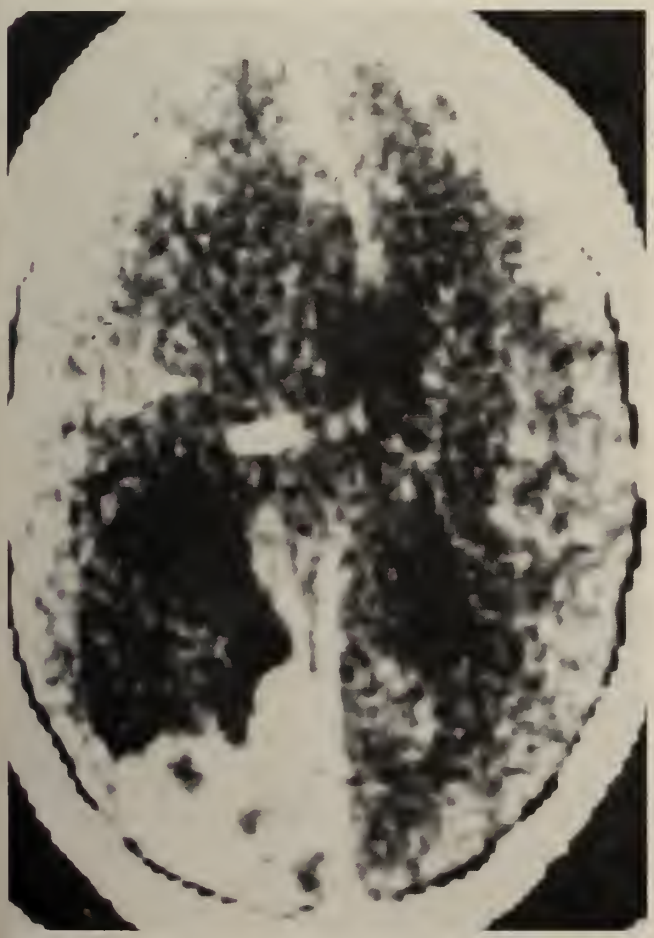

Figure 2.—The computed tomographic scan shows a mass in the left occipital region with a transfalcial shift.

Discussion

This case is only the second reported occurrence of cerebral metastases from a primary cardiac rhabdomyosarcoma. The left atrial location of the tumor and the surgical manipulation to remove it explain the access of the malignant cells to the systemic circulation and thus to the brain and the other sites of metastases found in this patient. Emboli originating in the left side of the heart generally involve the brain, the kidneys and the spleen, so that it is somewhat surprising that metastases in this case were not more widespread. Because primary rhabdomyosarcomas of the heart are rare, the distribution of their metastases is unknown and the likelihood of cerebral involvement is similarly unknown. Common sites of metastases from noncardiac rhabdomyosarcomas, however, are lungs, kidneys, heart, adrenals and mediastinum.[4] Cerebral metastases from rhabdomyosarcomas, regardless of primary site, are generally reported to be rare, although in one study,[5] cerebral metastases were reported in 4 of 15 patients with rhabdomyosarcomas.

Despite their apparent rarity, cerebral metastases should be considered in the differential diagnosis of neurologic symptoms in patients known to have rhabdomyosarcomas. This patient's neurologic problems were attributed initially to factors other than metastases from his cardiac rhabdomyosarcoma, as metastatic sarcoma in the brain is reported to be unusual. In the other reported case of cerebral metastases from a cardiac rhabdomyosarcoma, the patient, a 50-year-old woman with tachycardia and an apical murmur, suffered from what was considered to be multiple strokes. The diagnosis of cerebral metastases from a cardiac rhabdomyosarcoma was not made until the patient died and an autopsy revealed the primary tumor in the left auricle and left ventricle with cerebral metastases.[3] Similarly, a noncardiac rhabdomyosarcoma developed in a 14-year-old girl with neurologic symptoms without radiographic or electroencephalographic evidence of cerebral metastases.[6] The autopsy examination showed a circumscribed metastatic lesion in the frontal region. Cerebral metastases from rhabdomyosarcomas may produce equivocal neurologic signs and symptoms, and the diagnosis of cerebral metastases may not be clear from radiographic examinations. Additional autopsy studies would be helpful in determining the incidence of cerebral metastases from rhabdomyosarcomas and in correlating the presence and distribution of metastatic lesions with neurologic symptoms.

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Correspondence

Carpal Tunnel Syndrome

To the Editor: The article on carpal tunnel syndrome (CTS) by Barnhart and Rosenstock in the July issue[1] is to be acknowledged for focusing attention on this prevalent condition. Though the article increases the reader's awareness of this problem, it does not appear that the conclusions drawn by the authors are adequately supported by the study findings.

The authors indicated that selection bias was a limitation of their study, yet they did not appear to consider the potential effects of this bias in reaching their conclusions. Unlike the clustering of rare diseases cited in the study, the appearance of a clustering of patients with CTS in particular jobs does not necessarily indicate a relationship between the job and this condition. In order to answer epidemiologic questions of this type, one must review information on normal individuals as well as those who have an illness. I wonder whether the authors would have come to the same conclusions if they had randomly selected and reviewed workers from the total of 1,800 female checkers in the local union or if they had found a clustering of seven individuals with CTS from among a group of school teachers or attorneys.

Although this article presents some interesting information, and while its basic premise may be valid, it does not provide an objective and well-substantiated basis from which to arrive at its stated conclusions and inferences. The article adds to a growing body of literature on this subject that is based primarily on subjective clinical impressions, and emphasizes the need for objective, statistically sound, epidemiologic studies of workers in a variety of industrial settings to determine what relationship, if any, there is between occupation and CTS.

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Criteria for Brain Death

To the Editor: A discussion of brain death in the Epitomes section in the June 1987 issue[1] was somewhat disturbing. I am specifically referring to the inclusion of criterion 1, which states, "Irreversible structural damage to the CNS shown by computed tomographic scanning or magnetic resonance imaging." This statement, while somewhat nebulous, seems to imply that one must demonstrate irreversible structural damage to the brain by an imaging technique before the declaration of brain death can either be made or considered. This is clearly not a requirement of statute in most regions and, in fact, is impossible under certain circumstances where the brain is clearly dead.

In the circumstance of irreversible brain damage from hypoglycemia when the clinical criteria are met for brain death, one may see nothing using these imaging techniques, and it would be clearly inappropriate to wait until the brain demonstrates some of the changes one sees on imaging until such a declaration is made. Furthermore, in patients with severe head injury where structural damage is the rule rather than the exception, the presence of such computed tomographic or magnetic resonance imaging findings should not, and does not in most institutions, play any role in meeting criteria for brain death.

The statutes in most states have served us well in allowing us to determine brain death, and the inclusion of an additional criterion using neurodiagnostic imaging techniques, in my view at least, is clearly inappropriate. It adds nothing positive to the criteria that have evolved both as a result of the *ad hoc* committee of Harvard Medical School and the deliberations of other bodies. In fact, it is only likely to confuse further rather than clarify what the concept of brain death means.

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Soviet Medicine

To the Editor: To serious students of the Soviet medical bureaucracy, Dr David Friedenberg's brief review of the health care system in the Soviet Union in the August 1987 issue[1] is very disappointing. While it is admittedly difficult to provide a thorough overview of this large and important segment of Soviet society in a few pages, the conclusions he draws are misleading on several levels.

After a disclaimer that allegedly limits his observations to the Leningrad medical establishment, Friedenberg asserts that "the system is adequate to meet the needs of (the) people," and that "Soviet physicians seem to be pleased with the quality of care provided." He implies that these statements hold on a national level, which simply is not the case. Even in relatively privileged population centers such as Leningrad or Moscow, such conclusions are far from the mark, as the most elementary measures of physician performance make clear. He fails to mention, for example, that by dictum, Soviet physicians are required to see eight patients per hour in their Polyclinic duties (*Wall Street Journal*, Aug 18, 1987, p 1). After taking account of the 5 minutes for required paperwork on each patient, approximately 2.5 minutes are available for actual patient contact, unlikely to represent "quality" medical care by anyone's standards.

Soviet physicians are disgruntled and have virtually no incentive to provide good care, and such inadequacies are noted widely in the press. S. P. Burenkov, the recently deposed Minister of Health, has spoken of the "disastrous inertia and indifference" among medical personnel (*Meditsinskaya Gazeta*, 24 Oktyabrya, 1986, p 1) and proposed methods, now being considered as part of Gorbachev's *perestroika* (restructuring) campaign, to overcome these shortcomings. The reforms are mostly to be carried out through salary increases amounting to an average raise of 30% but, even so, the remuneration of physicians will be barely equal to that of an average laborer. This is consistent with the longstanding official Politburo classification of medical professionals amid the ranks of the "unproductive sectors" of the economy, from which their valuation is easily

inferred. It is little wonder that the practice of bribing physicians in order to insure adequate treatment is a major source of income for most Soviet doctors[2] and not merely limited to the "medical elite," as Friedenberg would have the reader believe.

From the individual patient's perspective, the Soviet health care system is at best an unfriendly monolith. There is little, if any, patient participation in the choice of treatment, thought by most practitioners to be vital to the therapeutic process. Indeed, patients with certain diagnoses, such as solid tissue tumors, *must* receive treatment, almost exclusively limited to surgical and radiation modalities. Thus, even avoiding potentially mutilating treatment is not an option in most circumstances.[3] Simple infection control and attention to nutritional needs are absent in most hospitals in the USSR.

On the broader level of public health measures, Soviet citizens have witnessed a decrease in average life expectancy during the period 1975 to 1985. Infant mortality figures have also risen during this time, placing the Soviet Union 50th among all nations in the world and the worst among the developed countries.

There are vast economic and political problems within the Soviet Union, to be sure, and there is little doubt of their adverse impact on Soviet health care. Compared to even more poorly financed health care systems, such as that of the People's Republic of China, the Soviet system cannot in any sense be viewed as a paragon of socialist success. Fundamental changes in the education of Soviet medical students and legal incentives for physician productivity will be required before the appalling decline in the general level of health care is reversed.

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Use and Safety of Miconazole During Pregnancy

To the Editor: The article by Chow and Jewesson on "Use and Safety of Antimicrobial Agents During Pregnancy" in the June 1987 issue[1] indicated that use of miconazole nitrate (Monistat) was relatively contraindicated during pregnancy. According to the 1987 *Physicians' Desk Reference*, there were no adverse effects noted or complications attributable to miconazole nitrate therapy in infants born to 514 pregnant women treated with the drug during pregnancy. The second edition of *Drugs in Pregnancy and Lactation*[2] places miconazole nitrate in the category of risk factor B, which indicates that animal reproductive studies have not demonstrated fetal risk, and controlled studies in pregnant women have not shown an adverse side effect. On the other hand, tetracycline is given a risk factor D in the same book, whereas in the article by Chow and Jewesson, tetracyclines are called relatively contraindicated, which would indicate that miconozole preparations have the same risk as tetracycline in pregnancy, which I don't think is supported by the literature.

I feel that we have enough problems involving liability with the use of medications during pregnancy without adding fuel to the fire by publishing an article suggesting that a very commonly used drug like Monistat has the same risks as a drug that we are very reluctant to use in pregnancy, tetracycline. I have seen no other published data that suggest a problem with the use of Monistat during pregnancy. Like anyone treating pregnant women, I am reluctant to use Monistat or any drug in the first trimester because of some concern about potential for teratogenicity. The use of Monistat certainly does not, in my experience, have the risk that is being given to it by the authors of this article.

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Drs Jewesson and Chow Respond

To the Editor: The topic of antimicrobial use during pregnancy remains relatively controversial and poorly understood. The decision to use an antimicrobial agent must always be made with consideration to both the potential benefits and the risks to mother and fetus. For only a small number of drugs do we have sufficient evidence to categorically state that their use is considered safe or that their toxicity outweighs any usefulness they might provide in a clinical setting. For the remaining agents, a judgment must be made based on an objective interpretation of the available literature. Such is the case with miconazole nitrate.

Dr Ainsworth correctly states that miconazole nitrate is frequently used in pregnant women and that this use does not appear to be associated with any apparent harm to mother or fetus. Indeed, Briggs and co-workers[1] consider miconazole nitrate to carry a risk factor category of B, implying that there are no controlled studies in women that demonstrate an adverse effect from this drug.

What Dr Ainsworth neglects to identify is that the available literature refers specifically to topical miconazole nitrate. In view of the fact that only small amounts of the drug are absorbed systemically when applied to the vagina for moniliasis, it is not surprising that a low incidence of overall adverse effects has been observed. However, our paper specifically addresses parenteral antimicrobials, and our recommendations pertain to the injectable form of miconazole nitrate only.

The safe use of miconazole nitrate injection in pregnancy has not yet been established.[3] Studies on nonpregnant patients have shown a high incidence of phlebitis, pruritus and rash in addition to several hematologic abnormalities (decreased hematocrit, thrombocytosis, leukopenia). A reversible hyperlipidemia has also been described, as well as hyponatremia and hypotension.[2] In view of these potentially serious complications, the authors classified the use in pregnancy as "relatively contraindicated." As with all other drugs in this general category, careful consideration of potential toxicities and alternate agents must be made before use of the drug is initiated.

We would concur with Dr Ainsworth that topical miconazole nitrate is probably a safe agent to administer to a pregnant patient (as is topical nystatin), and that this use can be categorized as "use with caution." However, we

stand by our original classification of "relatively contraindicated" for injectable miconazole nitrate in view of the known and potentially serious toxicities and the unknown effects on the pregnant patient and the fetus.

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Condom Use, Not Barrier Method, To Prevent Heterosexual HIV Infection

To the Editor: George Rutherford, MD, and colleagues presented a comprehensive discussion of perinatal human immunodeficiency virus infection (HIV) in the July 1987 issue.[1] They made a statement that we wish to clarify because of the ambiguity of the term "barrier contraceptive."

"Regardless of other contraceptive methods used, they should use barrier methods of contraception—such as a condom or a condom plus a diaphragm with a nonoxynol-9-containing spermicide—during intercourse to diminish the chances both of transmitting HIV to their sexual partners and of being reinfected with it."[1]

Although there is some evidence that the condom decreases the rate of HIV infection,[2,3] there is no evidence to indicate that a diaphragm is protective. The diaphragm, used without a condom, will not prevent skin-to-vaginal mucosal contact and may not prevent contact with cervical secretions[4] or semen. The mode of heterosexual transmission from male to female or vice versa is not understood. It is not known if transmission from male to female is more efficient when virus contacts the vaginal squamous epithelium or endocervical glandular epithelium.

We should advise people that regardless of the contraceptive method used, a condom should be used with nonoxynol-9-containing spermicide, using correct technique.[5] If a couple chooses to use a diaphragm in addition to the condom and spermicide, they will have more effective contraception, but the combination may not protect them better against HIV infection.

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'Screening' and 'Routine' Testing

To the Editor: One article[1] and two Epitomes of Internal Medicine[2,3] in the September 1987 issue suggest that screening or "routine" testing is worthless in hospital admissions. Unfortunately, the authors fail to recognize the basic difference between screening and tests done at the time of a hospital admission. Blue Cross, Blue Shield and even the American College of Physicians have made the same mistake. It is time to correct this!

Screening is performed on healthy people to detect clinically inapparent disease; the purpose may be to minimize an insurance company's risk or to protect the public, as in screening blood donors for hepatitis or human immunodeficiency virus infection. The main goal of screening is not necessarily related to an individual's health and, admittedly, screening is unsuccessful in finding unrecognized disease.

Admission laboratory testing, by contrast, is performed on an unhealthy person at the time of a hospitalization in order to confirm a diagnosis, to rule out other diagnoses or complications and, most important, to establish a baseline of physiologic parameters so that the effects of our subsequent diagnostic, therapeutic or surgical interventions may be sensibly evaluated. Admission testing is not done to detect clinically unsuspected disease but, ironically, is more successful than screening in finding such because hospitalized patients are older and are more likely to have multiple conditions.

The lack of appreciation of the difference between screening and admission testing has led to the suggestion that admission testing be restricted in order to save money. It would not be inconceivable that Blue Cross/Blue Shield would next suggest that internists and other primary care physicians could save money by restricting a history to the "present illness" and confining physical examination to the suspect organ. Let us beware of such absurdities in both clinical and laboratory medicine.

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3. Loo LK: 'Routine' preoperative laboratory testing. West J Med 1987; 147:322-323

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To the Editor: In the September 1987 issue Rucker and co-workers continue their assault on laboratory testing by arguing that screening electrolyte, blood urea nitrogen and glucose level determinations are not indicated when patients are admitted to hospital.[1] Two Epitomes[2,3] as well as an editorial[4] beatify this study by implying that it represents a significant advance in internal medicine, along with the authors' previous study of urinalysis.[5]

In fact, the study does not break new ground; rather, it sets up a straw man. Although the practice may, indeed, be prevalent, I know of no reputable authority that currently recommends screening of this type in patients admitted to hospital.[6] Any sensible physician will restrict the ordering of the cited tests to patients with findings such as those listed by the authors. One must assume that all six tests were obtained in their center in so many instances because the testing instrument or

the laboratory order form, or both, provided all automatically. With such an instrument available, providing all rather than those actually required may well be cost effective.[6]

Although the authors have undoubtedly documented an abuse of laboratory testing, it is questionable whether curbing such screening will substantially reduce laboratory costs. The marginal cost of large volume testing on automated equipment, if ordered in batches, is minimal. Indeed, unit costs are heavily volume-dependent and may increase significantly if fewer tests are ordered (the analogy to fares in public transit systems is apt). In my experience, far more expensive abuses include excessive repetition of testing and the ordering of large numbers—often redundant panels—of expensive exotic tests in pursuit of "zebras."

It is noteworthy that house officers (who actually request the tests) are ordering these screening panels in a higher proportion of patients admitted to the authors' medical center than they order urinalyses, despite the apparent greater yield of a urinalysis (I am pleased to note that the authors no longer refer to these as "routine").[1,5] Why are they doing so? Is it possible that their instruction is faulty? Or could it be that, to these young physicians, actions speak louder than words? Could Rucker and co-workers, their role models, be guilty of a "don't do as I do, do as I say" attitude?

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Phosphorus and Water

To the Editor: In the article "Emergent Management of Chemical Burns," extracted from *Audio-Digest Emergency Medicine*, in the September issue,[1] an erroneous statement regarding the chemical behavior of white phosporus was made. The article states, "White phosphorus is a material that basically ignites when exposed to water." White phosphorus is stored in water because it ignites easily in air.[2] Sodium metal, as the article states, reacts with water and is appropriately stored in oil.

If white phosphorus should come in contact with the skin, washing the area with a 2% solution of copper sulfate has been suggested, although the absorption of copper may be a complication.[3] Rather than covering the wound with oil, as recommended in the extract, the exposed area should be kept thoroughly moist with water until debridement or some other form of treatment can be instituted.

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More Insects in the Operating Room

To the Editor: A letter to the Editor, "Insects in the Operating Room," by Sherman and co-workers appeared in the September 1987 issue,[1] which arrived several days after the *American Medical News* arrived. The *American Medical News* documented Dr William Burman's interesting approach to dealing with insects in the operating room:[2] he bottled those he detected and sent them to the hospital administrator! Evidently, it was his belief that the insects were permanent residents in the hospital and had not come in with a patient.

Sherman and colleagues describe arresting the trespasser by the "surgical technique known as 'squashing.'" As a family physician I want to make sure that this technique is not entirely expropriated by surgical colleagues. After all it does seem to involve the "whole bug."

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Health Care Delivery

Categorization of Hospital Emergency Services—Developing Valid Criteria

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In a pilot project sponsored by the California State Emergency Medical Services Authority, validated, verifiable criteria were developed for the vertical categorization of hospital emergency services in 11 different groupings of medical and surgical emergencies. We describe the development of an assessment process and categorization criteria to identify the most appropriate receiving facility for interfacility transfer and, in selected instances, field triage of patients with different levels of severity of illness or injury. We propose that this facility assessment project be used in the critical care planning process for the eventual vertical categorization of hospital emergency services in California and as a template for similar projects in other states.

(Riner RM, Collins KM, Foulke GE, et al: Categorization of hospital emergency services—Developing valid criteria. West J Med 1987 Nov; 147:602-608)

The categorization of hospital emergency services (CHES) is the process of assessing and categorizing the relative preparedness and capabilities of hospitals (or other health care facilities) and their medical staffs to provide emergency medical care and associated health care services to patients with various types of medical and surgical emergencies. The concept was first proposed in 1966 by the National Academy of Sciences' National Research Council in its report, "Accidental Death and Disability: The Neglected Disease of Modern Society,"[1] as a mechanism for matching critically ill or injured patients with the appropriate health care facilities.[4]

Since then, CHES has evolved in three related but distinct directions: horizontal categorization, vertical categorization and designation. Horizontal categorization is assessing and classifying a hospital's capability to manage any and all types of medical and traumatic emergencies. Vertical categorization results in a separate classification of each of a hospital's services for specific types of medical and traumatic emergencies. Designation is the process of franchising a limited number of "centers of excellence" (such as trauma centers and burn centers) for the care of the critically ill or injured in the context of "regionalization" of emergency medical services (EMS).[2] We describe the methodology used to develop, refine and internally validate the criteria and the process for vertically categorizing hospital emergency services in California.

The history of national CHES efforts is thoroughly detailed in the chapter on emergency department categorization in *The Hospital's Role in Emergency Medical Service Systems* by Cross and Riggs[3] and in articles by Hampton,[4,5] Salguero[6] and others. In 1969 the American Society of Anesthesiologists recommended that the National Research Council's Categorization Guidelines, which emphasized trauma, be expanded to encompass all life-threatening injuries. The Commission on Emergency Medical Services of the American Medical Association (AMA) developed in 1971 its own set of CHES guidelines,[7] which were later endorsed by the American Hospital Association[3] and implemented in a number of state and regional EMS programs. In California, horizontal categorization criteria were incorporated into legislation—Title 22, Division 5, of the California Administrative Code—regulating special permit services provided by general acute care hospitals. The emergency departments of California hospitals are licensed as "comprehensive," "basic" or "standby" based on emergency department and in-house services, equipment and staffing.

CHES was originally proposed as a framework for matching patients who had different degrees of medical emergencies with hospitals providing different levels of emergency medical services. In California, however, CHES has generally played a limited role in patient triage. This reflects the limitations of horizontal categorization programs, which typically fail to acknowledge that hospitals often specialize, providing different levels of service to different types of patients.[4]

Recognizing the need to address the realities of hospital specialization, the AMA released, in 1980, a set of vertical categorization criteria for each of eight groupings of emergency patients—acute medical, behavioral, burn, cardiac, neonatal and pediatric, poisoning, spinal cord injury and general trauma.[8] The primary objective of this program was to identify regional centers for the care of critically ill or injured patients or patients requiring highly specialized services,[6] and it was also promoted as a more effective means of matching patients to the most appropriate facility and expediting "up-the-line" transfers of patients in critical condition.[9]

In California, the State EMS Authority, mandated by law to develop guidelines for "facility assessment," funded a

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ABBREVIATIONS USED IN TEXT

AMA = American Medical Association
CHES = categorization of hospital emergency services
EMS = emergency medical services

project for the development of vertical CHES that was piloted in the Sierra-Sacramento Valley and the northern California EMS regions in 1983. The stated goals were to inventory the services provided in the regions' facilities and to indicate appropriate patient-receiving points based on hospital capability. These goals were consistent with the State EMS Authority's recommendations that EMS agencies provide information that can be used by physicians, hospitals and hospital associations so that these providers can make informed decisions about how to develop, organize and appropriately use health care resources in the EMS system. In California, EMS agencies have a legislative mandate to ensure that patients with medical emergencies are provided with services adequate to meet their needs, if these services are readily available.

One way for EMS agencies to comply with this mandate is to facilitate the appropriate transfer of patients from one hospital to another. This can be accomplished by providing information about the capabilities of possible receiving hospitals to a referring physician, who has a legal obligation to ensure that the chosen hospital can effectively manage a patient's problem,[3,10] and by encouraging the development of interfacility transfer agreements. Finally, EMS agencies can develop and implement field-triage criteria that route patients to the closest, most appropriate facility, though considerations such as patient preference and prepaid health plan participation limit the use of this type of triage to those most severely ill and injured patients for whom timely access to definitive care is vital.

Following completion of the CHES pilot project, the California State EMS Authority required all regional EMS agencies applying to the state for (federal grant) EMS development funds to assess the critical care services available in their area as a part of the EMS planning process. State EMS regulations, however, do not require these agencies to follow the assessment guidelines provided by the authority.

The staff of the Alpine, Mother Lode, San Joaquin EMS Agency (eight counties) examined the authority's CHES pilot project and other categorization schemes—including the AMA's Emergency Medical Services Commission's criteria—and identified a number of deficiencies common to all. Some of the criticisms leveled at the AMA's horizontal CHES scheme, as outlined in appendix A of Hampton's progress report,[4] seemed to apply equally well to the various vertical CHES criteria and processes the staff reviewed. These programs often relied on criteria that were vague or insufficiently discriminating (such as the term "promptly available"), or unrealistic (the requirement for comprehensive in-house blood banks). In addition, the criteria appeared to be skewed towards large university teaching hospitals and difficult if not impossible to verify, even with an extensive audit of medical records. For example, the pilot project in California relied heavily on an estimate by hospitals of the availability of various on-call staff specialists—available within 30 minutes more than 90%, 75% to 89%, 50% to 74% or 0% of the time—to distinguish between levels of service. The use of nonverifiable CHES criteria has been cited as one reason why previous categorization efforts have at times seemed more reflective of self-interest than objective accuracy.[11] Salguero[6] provided a detailed account of the process used in Pennsylvania to develop CHES criteria and lists of related clinical conditions. He described some of the difficult and at times obscure considerations, such as those involving physicians' commitments to hospital critical care services, that are a part of CHES criteria development. The most telling deficiency of CHES programs is the lack of independent validation of the criteria (other than through the consensus of the experts who helped develop them).

The agency staff felt that, to be considered a valid framework for patient triage, CHES criteria should reflect the standard of hospital practice in the community, make distinctions between levels of service that reflect the actual distribution of patients and existing resources, acknowledging the role of hospital specialization in critical care services and be easily verified. The final step in the validation of the CHES criteria and the triage process, a demonstrable reduction in morbidity and mortality, inappropriate or delayed transfers and (if field triage is implemented) urban interfacility emergency transfers, can only be accomplished after the program is implemented. Although the American College of Surgeons' criteria for trauma center designation[12] have been validated concurrently by a number of trauma-outcome studies, it is not entirely clear if any of the individual criteria have actually been validated as appropriate indicators of the level of commitment to trauma care or as essential ingredients for the survival of major trauma victims. This may be why some of the designation criteria in the trauma care system regulations for the state of California have been hotly debated in EMS Commission hearings. The agency staff decided to approach vertical CHES from several perspectives: reorganizing the categories for level of service (comprehensive, major and so forth) to reflect the inherent distinctions between hospitals in California, redefining the clinical groupings (trauma, burns and the like) to reflect trends in hospital specialization, revising categorization criteria to reflect actual hospital practice (while considering the need for verifiability) and revising the lists of clinical conditions so that they would reflect the new criteria and support transfer triage and eventually field triage. A procedure was established to test the criteria and process (validation steps listed above) through the cooperation and assistance of the California State EMS Authority and five other regional EMS agencies representing a total of 36 counties and 116 participating hospitals in the six EMS regions.

The initial package, called the Facility Assessment Project, included a set of nine clinical groupings (later expanded to 11; see Table 1), each organized into four levels of emergency service capability: comprehensive, major, general and basic. Comprehensive (level C) services were subdivided into two subcategories representing the distinction between large research-oriented, university-affiliated urban teaching hospitals (C′) and medium-sized to large community hospitals (with or without residency programs) committed to provide specialized critical care services to patients in the particular clinical grouping (C). The agency staff used established criteria wherever possible, such as the criteria for licensing of basic, supplemental and special permit services for hospitals in Title 22, Division 5, of the State of California Administrative Code, the standards and criteria developed by the California Children's Services Division of the State Department of Health Services for tertiary and intermediate neo-

natal intensive care units and the Los Angeles Pediatric Society and the Los Angeles County Department of Health Services criteria for "emergency departments approved for pediatrics." Many of the standards for level I and level II trauma centers were integrated into the criteria, although maintaining the distinction between "assessment" (that is, capability) and "designation" (that is, franchising) required that the assessment criteria be less stringent than the designation criteria.

Responses from 116 hospitals to the self-assessment instrument were entered into a computer data base, and each criterion was independently tested by identifying the hospitals that lacked five or fewer criteria to move up one level (in each of the nine clinical groups), listing these criteria and collating the frequency with which each of the 629 criteria in the pilot project appeared on these lists. This process identified 151 "suspect" criteria that merited further scrutiny.

At this point, a verification team composed of a surgeon, an emergency physician, an emergency department nurse and a hospital administrator was recruited. This team visited all 26 of the hospitals in the Alpine, Mother Lode, San Joaquin EMS region to verify the responses of the hospitals to the self-assessment instrument. The team members, in conjunction with a six-region subcommittee, reviewed all of the facility assessment criteria in light of the computerized scoring and validation process and the information gained from the site visits. As a result of this review, about 20% of the "suspect" criteria were validated, 25% were rephrased in the self-assessment instrument, 22% were eliminated, 8% were adjusted to a different assessment level and 25% were refined (a combination of the above). The review committee also identified an additional 16 criteria that were not flagged by the computerized validation process but which, based on the site visits, merited reconsideration.

The results of the facility assessment process in the Alpine, Mother Lode, San Joaquin EMS Region are presented in Table 1. This table clearly shows the range and depth—and specialization—of hospital emergency services in the region. The table also shows that certain emergency services, such as those for managing trauma or exposure to radiation or hazardous materials, may need further development in the region.

An example of the resultant criteria (for cardiovascular or pulmonary emergencies) is presented in Table 2. The original set of criteria for this category of illnesses included the requirement for comprehensive in-house blood banks for level C and C′ facilities. The pilot study showed that few of the hospitals that would otherwise have met these level C or C′ criteria had comprehensive blood banks, though all had significant amounts of blood stored in-house and replenished from blood banks outside the facility. As a consequence, the criteria were revised (Table 2, item numbers 6105, 6110 and 6115) to reflect this standard of practice. For similar reasons, the initial criteria requiring "central station cardiac monitoring" in the emergency departments in level M, C and C′ facilities were revised (Table 2, item No. 2020) to accommodate a wider range of options for meeting the need for continuous cardiac monitoring of seriously ill cardiac patients. The issue of on-call-physician availability for each specialty at each of the four levels of service was carefully considered and subjected to the same test of standard of practice. The resultant criteria provide varying degrees of assurance of specialist

TABLE 1.—*Facility Assessment of 26 Hospitals in the Alpine, Mother Lode, San Joaquin EMS Region*

	Emergency Services										
Hospital	*Cardiovascular/ Pulmonary*	*General Trauma*	*Pediatric*	*Burn*	*Spinal Injury*	*Poison*	*Psychiatric*	*Radiation/ Toxin*	*Amputations*	*Obstetric*	*Neonatal*
1	General	General	General	General	General	General	General	Basic	General	Basic	Basic
2	General	General	General	General	General	General	General	Basic	General	General	General
3	General	Basic	Basic	Basic	Basic	General	General	Basic	Basic	Basic	Basic
4	General	General	General	General	General	General	Basic	Basic	General	Basic	Basic
5	Basic	Basic	Basic	Basic	Basic	Basic	Basic	Basic	Basic	Basic	Basic
6	General	General	General	General	General	General	General	Basic	General	General	General
7	Major	General	Major	Major	General	Major	General	Major	General	Major	Major
8	General	General	General	General	General	Major	Basic	Basic	General	Major	General
9	General	Basic	Basic	Basic	Basic	Basic	Basic	Basic	Basic	Basic	Basic
10*											
11	Major	Major	General	General	General	General	General	Basic	Major	General	General
12	Major	Major	Major	Major	General	General	General	General	Major	Major	General
13	General	General	General	General	General	General	General	Basic	General	Basic	Basic
14	Compr	Major	Major	Major	Major	Compr	Major	Major	Major	Major	Major
15	Major	Compr	Major	Major	Major	Compr	Compr	Basic	Major	Compr	Compr
16	Major	General	Major	Major	General	Major	General	General	General	General	General
17	General	General	General	General	Basic	General	Basic	Basic	Basic	General	General
18	Compr	Major	Compr	Major	Major	Major	General	Major	Major	Major	Major
19	Major	General	Major	Major	General	Major	Major	Basic	General	Major	General
20	Major	General	General	Major	General	Major	Compr	Major	General	Basic	Basic
21	Major	Major	Major	Major	Major	Major	Compr	Major	Major	Major	Major
22	Major	General	Major	General	General	Major	Basic	Basic	General	Compr	Compr
23	General	General	General	General	General	Major	General	Basic	General	General	General
24	Major	General	General	General	General	General	Major	Basic	General	Basic	Basic
25	General	General	General	General	General	Major	General	General	General	Major	Major
26	General	General	General	General	General	General	General	General	General	Basic	Basic

Compr=Comprehensive, EMS=Emergency Medical Services

*This hospital declined to release results of the facility assessment to the public

TABLE 2.—*Specific Criteria Developed for Cardiopulmonary Emergency Medical Services Using the Facility Assessment Process*

Clinical Condition	*Item No.*†	*Emergency Services** B	G	M	C	C′
Licensed basic services‡	1030	...	x	x	x	x
Supplemental services						
Special permit required§						
Comprehensive emergency medical service (except 70453 j,m-r)	1040	...	...	...	...	x
Basic emergency medical service—physician on duty (except 70413 m)	1045	...	...	x	x	...
Standby emergency medical service—physician on call; additional features required for cardiopulmonary emergency care	1050	...	x	...	...	...
Cardiac monitors with automatic dysrhythmia alert or a policy for cardiac monitoring capability with a 1:1 ratio	2020	...	...	x	x	x
Apparatus to establish intra-arterial blood pressure monitoring	2030	...	...	x	x	...
Pneumatic antishock trousers	2035	...	...	x	x	x
Two-way radio linked with vehicles of emergency medical services transport system	2040	...	...	x	x	x
Cardiovascular surgery service‖	1035	...	...	...	x	x
Special permit not required¶						
Intensive care service—additional features required for cardiopulmonary emergency care	1090			x	x	x
Cardiac output monitoring	3005	...	...	...	x	x
Electronic cardiopulmonary pressure monitoring	3010	...	...	...	x	x
Patient weighing devices	3015	...	...	x	x	x
Pulmonary function measuring devices	3020	...	...	x	x	x
Intracranial pressure monitoring equipment	3025	...	...	...	x	x
Bedside circulatory assist device (aortic balloon pump)	3030	...	...	...	x	x
Temporary transvenous pacemaker equipment	3045	...	...	x	x	x
Coronary care service—additional features as described in intensive care service (except circulatory assist device) may be combined in CCU-ICU area	1080	...	...	x	x	x
	or 3075	...	...	x	...	...
Hemodialysis service						
Acute hemodialysis capability in-house 24 h/day availability	1140	...	...	...	x	x
Inpatient hemodialysis services limited availability	1140 or 1145	...	...	x	...	...
Rehabilitation center or cardiac rehabilitation service provided by dedicated rehabilitation staff under the direction of a physician and supported by physical therapy, social services or cardiac rehabilitation services psychologist and occupational therapy personnel, services initiated in-house (these may be provided by contract)	1120 or 1155	...	...	x	x	x
Nuclear medicine service—additional features for cardiopulmonary emergencies	1095	...	...	x	x	x
Ventilation—perfusion lung scan capabilities	7065	...	...	x	x	x
Thallium scanning capabilities	7070	...	...	...	x	x
Respiratory care service#	1125	...	...	x	x	x
Additional features and capabilities within licensed basic services						
Operating suite						
Staffing promptly available in-house or on call (within 30 min, 24 h/day by written policy)	4110 or 4115	...	...	x	x	x
Monitoring equipment	4095	...	...	x	x	x
Cardiopulmonary bypass oxygenator (team available within 30 min by written policy)	4130	...	...	...	x	x
Operating microscope	4015	...	...	...	x	x
Thermal control equipment for patient and blood	4035	...	...	x	x	x
X-ray capability	4020	...	...	x	x	x
Endoscopes, including scopes for mediastinoscopy, gastroscopy, colonoscopy and flexible bronchoscopy	4025	...	...	x	x	x
Clinical laboratory service—available 24 h/day						
Coagulation studies within 4 h	6125	...	...	x	x	...
Access to whole blood within 1 h	6105	...	x	x	x	x
In-house blood supply of at least 25 units	6115	...	...	...	x	x
In-house blood supply of at least 12 units	6115	...	...	x	...	...
In-house supply of platelets and fresh frozen plasma	6110	...	...	...	x	x
Blood gas and pH determination within 30 min	6120	...	...	x	x	x
Serum and urine osmolarity within 4 h	6020	...	...	...	x	x
Serum and urine osmolarity within 24 h	6020 or 6021	...	...	x	...	...

CCU=coronary care unit, ICU=intensive care unit

*The emergency services are organized as follows: B = basic, G = general, M = major, C = comprehensive (community hospital with or without residency), C′ = comprehensive (university-affiliated urban teaching and research facility).

†Item numbers refer to self-assessment instrument

‡Medical, surgical, nursing, anesthesia, clinical laboratory, radiologic, pharmaceutic and dietary services meeting all criteria in article 3 of Title 33, Division 5, Chapter 1 of the State of California Administrative Code.

§In accordance with Article 5 and meeting all criteria in Article 6

‖Currently meeting minimum service base support criteria in accordance with §70433 of 260 cardiac catheterizations and 150 cardiovascular procedures per year requiring extracorporeal bypass.

¶Meeting all criteria in Article 6.

#Per §70615 to §70623.

**Numbers in parentheses signify minimum number of specialists routinely participating in emergency department on-call schedule.

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TABLE 2.—*Specific Criteria Developed for Cardiopulmonary Emergency Medical Services Using the Facility Assessment Process*

Clinical Condition	Item No.†	Emergency Services* B	G	M	C	C′
Quantitative analysis of cardioactive drug within 6 h						
Digoxin	6035	...	...	x	x	x
Lidocaine hydrochloride	6040	...	...	x	x	x
Procainamide hydrochloride	6045	...	...	x	x	x
Phenytoin (Dilantin)	6050	...	...	x	x	x
Phenobarbital	6055	...	...	x	x	x
Theophylline	6060	...	...	x	x	x
Antibiotic level monitoring for tobramycin and/or gentamicin sulfate	6100	...	...	x	x	x
Radiologic/special capabilities						
Angiography, peripheral vascular	7025	...	...	x	x	x
Sonography	7040	...	...	x	x	x
Echocardiography	7050	...	...	...	x	x
Stress testing	7055	...	...	...	x	x
Computed tomography, body	7035	...	...	...	x	x
Postanesthetic recovery room	5000	...	...	...	x	x
Surgical ICU is acceptable	5000 or 5005	...	...	x	...	...
Registered nurses and other essential personnel available within 30 min, 24 h a day by written policy	5010 or 5015	...	...	...	x	x
Programs for quality assurance						
Cardiopulmonary care evaluation, including						
Specific audits for cardiopulmonary patients	9000	...	...	...	x	x
Multidisciplinary cardiopulmonary conferences	9055	...	...	...	x	x
Nursing care audits	9110	...	...	x	x	x
Program of periodic and timely outcome studies compared to state or national standards	9115	...	...	...	x	x
Cardiac research program						
Full cardiac research and training center services including residency training programs in cardiology and/or cardiovascular surgery	10000	...	...	...	...	x
Training program						
Formal programs in continuing education provided by hospital for physicians, nurses and allied health personnel	8000	...	...	x	x	x
Specialist availability						
Medical services/divisions/sections/committees (each staffed by qualified specialists)						
Anesthesiology	11010	...	...	...	x	x
Cardiology	11015	...	...	...	x	x
Emergency medicine	11035	...	...	x	x	x
Endocrinology	11040	...	...	...	...	x
Gastroenterology	11050	...	...	...	...	x
Hematology	11060	...	...	...	...	x
Immunology/rheumatology	11065	...	...	...	...	x
Infectious diseases	11070	...	...	...	...	x
Internal medicine (medicine)	11075	...	...	x	x	x
Nephrology	11085	...	...	...	...	x
Pulmonary diseases	11160	...	...	...	...	x
In-house						
In-hospital 24 h/day, 7 days a week. This requirement may be fulfilled by residents or other in-house (nonemergency department) physicians with special competence in the care of emergencies relevant to that specialty as judged by the chief of the respective service with qualified attending staff specialists on call and promptly available for consultations and on-site supervision. Note: General surgery residents must have completed at least 3 years of residency to fulfill this requirement						
Anesthesiology	12000	...	...	...	...	x
Internal medicine	12035	...	...	...	...	x
Emergency medicine	12020	...	...	x	x	x
General surgery	12030	...	...	...	...	x

CCU=coronary care unit, ICU=intensive care unit

*The emergency services are organized as follows: B = basic, G = general, M = major, C = comprehensive (community hospital with or without residency), C′ = comprehensive (university-affiliated urban teaching and research facility).

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TABLE 2.—*Specific Criteria Developed for Cardiopulmonary Emergency Medical Services Using the Facility Assessment Process*

Clinical Condition	Item No.†	Emergency Services* B	G	M	C	C′
In-house or on call and immediately available						
Cardiologist or specialists in intensive care on call and immediately available 24 h/day to provide intensive care services and cardiac catheterization to critically ill cardiac patients and intensive care unit coordination and supervision, with a minimum of four cardiologists or intensive care specialists on staff and routinely participating in cardiology call	12195	...	...	...	x	x
Normally promptly available						
In-house or on call 24 h/day, 7 days a week, and listed on the emergency department call list with a minimum number of specialists in each category on staff and routinely participating in the call schedule						
Anesthesiology (3)**	12000	...	...	x	x	...
Nurse anesthetist under physician direction (2)	12000 or 12175	...	x	...	...	...
Cardiac surgery (3)	12005	...	...	...	x	x
Cardiology (3)	12010	...	...	x	...	...
Endocrinology (2)	12105	...	...	...	...	x
Gastroenterology (2)	12110	...	...	x	x	x
General surgery (3)	12030	...	...	x	x	...
Gynecologic surgery (3)	12050	...	...	...	...	x
Hematology (2)	12115	...	...	...	x	x
Immunology (2)	12120	...	...	...	...	x
Internal medicine (3)	12035	...	...	x	...	...
Nephrology (2)	12130	...	...	...	x	x
Neurologic surgery (3)	12045	...	...	...	x	x
Neurology (3)	12040	...	...	...	x	x
Neuroradiology (2)	12140	...	...	...	...	x
Orthopedic surgery (3)	12060	...	...	...	...	x
Pathology (2)	12145	...	...	x	x	x
Psychiatry (3)	12075	...	...	...	...	x
Pulmonary diseases (2)	12165	...	...	...	x	x
Radiology (3)	12090	...	...	x	x	x
Urologic surgery (3)	12085	...	...	...	x	x
Pediatrics (3)	12070	...	...	x	x	x
Family practice or internal medicine (3)	12025 or 12035	...	x	...	...	...

CCU = coronary care unit, ICU = intensive care unit

*The emergency services are organized as follows: B = basic, G = general, M = major, C = comprehensive (community hospital with or without residency), C′ = comprehensive (university-affiliated urban teaching and research facility).

†Item numbers refer to self-assessment instrument

‡Medical, surgical, nursing, anesthesia, clinical laboratory, radiologic, pharmaceutic and dietary services meeting all criteria in article 3 of Title 33, Division 5, Chapter 1 of the State of California Administrative Code.

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**Numbers in parentheses signify minimum number of specialists routinely participating in emergency department on-call schedule.

availability based on verifiable on-call lists, yet accommodate a wide variety of arrangements for providing this on-call coverage. The initial lists of clinical conditions were also revised (see example, Table 3) to reflect changes in the criteria and, thus, existing trends in hospital practice. This listing of clinical conditions focuses on differentiating those patients who may need to be transferred to another hospital based on the nature and severity of their problems and the capability of the initial receiving hospital.

Additional work needs to be done to develop field-triage criteria, based on the facility assessment categorization scheme, which could be used by EMS personnel to triage selected patients in the field to the closest, most appropriate facility. It is clear that some clinical groupings, such as patients with burn and trauma emergencies, can be handled using field-triage criteria, whereas others, such as those with cardiopulmonary emergencies, may be very difficult to field-triage appropriately.

The California State EMS Authority has been authorized by Division 2.5 of the California Health and Safety Code to establish guidelines for utilizing hospital facilities according to critical care capabilities and for assessing hospitals and critical care centers. The EMS Authority is now in the process of developing facility assessment guidelines for consideration and review by hospital councils in California, local EMS agencies and the state EMS commission. In addition, mechanisms to audit the consequences of implementing facility assessment, on the appropriateness of interfacility transfer and eventually field triage and, finally, on morbidity and mortality need to be explored.

It has been said that any plan that might adversely affect emergency department use is seen as a threat to many hospitals regardless of the apparent soundness of the CHES concept from a medical standpoint.[3] For this reason, implementing the facility assessment process in California may not be easy. Categorizing hospital emergency services is, however, the

task that is most frequently omitted from overall EMS planning efforts.[13] CHES also has the potential to be used in a nonregulatory and nonpunitive way to solve the problem of "inappropriate" transfers through promoting transfer agreements and through criteria-based auditing. The facility assessment project described here can also provide hospital administrators with an assessment tool they can use to help determine the hospital's goals and objectives and to delineate the hospital's present and future role in providing emergency medical services.[13] It also provides local EMS agencies and departments with a mechanism for fine-tuning the assessment criteria and triage guidelines to meet local needs and regional standards of practice. The project enables these agencies to view services for emergency cases in their community as a whole and from the perspective of individual facilities and to integrate critical care and other hospital-based resources into the emergency medical services planning process.[11]

TABLE 3.—*Clinical Conditions Associated With Assessment Level**

Cardiopulmonary Emergencies
Level C—Comprehensive Medical Care
Probable dissecting aneurysm with obvious pulse deficit
Postresuscitation from pulseless rhythm: comatose
Symptomatic heart block requiring permanent pacemaker
Pump failure requiring circulatory assist device
Refractory symptomatic dysrhythmias
Possible rupture of papillary muscle, septum or ventricular wall
Emergency cardiac catheterization or open-heart operation
Level M—Major Medical Care
Severe nontraumatic shock
Severe ischemic chest pain
Respiratory failure requiring prolonged ventilator management
Congestive heart failure, severe
Drowning
Severe focal neurologic deficits that merit aggressive management
Probable pulmonary embolism
Level G—General Medical Care
Possible myocardial infarction (if CCU available)
Angina responsive to therapy
Responsive dysrhythmias
Asthma or chronic obstructive pulmonary disease requiring inpatient care
Near drowning
Level B—Basic Medical Care
Outpatient management indicated

CCU=coronary care unit

*This list of clinical conditions associated with each facility assessment level (from basic to comprehensive) shows the services routinely and predictably available in hospitals in each category. Frequently patients with problems like those listed in the level C category can (or must) be effectively managed in level M or even level G hospitals, depending on the circumstances and on available resources. If the physician responsible for the care of a patient determines that it is in the patient's best interests to be transferred to another facility, the above list may be used, along with all other pertinent considerations, when determining the most appropriate receiving facility. Because these other considerations may be paramount, this list should be used as a "rule of thumb," not as a standard of practice.

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Sufficiency of Clinical Literature on the Appropriate Uses of Six Medical and Surgical Procedures

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We reviewed the English-language clinical literature on carotid endarterectomy, cholecystectomy, upper gastrointestinal endoscopy, colonoscopy, coronary angiography and coronary artery bypass graft procedure to identify the appropriateness of using these procedures in 1981. Most of the 803 relevant articles and textbooks were published after 1975; about 10% of the 571 research studies were randomized, controlled trials, while two thirds were retrospective studies. Incomplete or contradictory information was available on the indications for and efficacy of using the procedures; almost no data were available on costs and use; data on complications failed to specify patients' symptoms or the relationship between complications and reasons for doing the procedure.

(Fink A, Brook RH, Kosecoff J, et al: Sufficiency of clinical literature on the appropriate uses of six medical and surgical procedures. West J Med Nov; 147:609-614)

Contemporary methods of containing rising medical costs in the developed world have been based on economic rather than medical principles, and their focus has been on allocating health funds on a geographic basis, prepaying hospitals, setting limits on physicians' fees or changing health insurance plans and benefits. Such methods, we assert, are inadequate because of their failure to distinguish efficiently between effective and ineffective care.[1] Could a combined clinical-epidemiologic approach to cost containment produce better health at similar levels of cost?

The clinical-epidemiologic approach strives to separate, in medically meaningful ways, appropriate from inappropriate uses of diagnostic and therapeutic procedures. When a procedure is appropriately used, expected health benefits (increased life expectancy, relief of pain, reduction in anxiety and improved functional capacity) meaningfully exceed expected negative consequences (mortality, morbidity, anxiety of anticipating the procedure). An underlying assumption of this approach is that physicians can identify and subsequently eliminate inappropriate use, and this will result in a better use of health funds.

One purpose of the medical literature should be to help physicians distinguish between the appropriate and inappropriate use of procedures. In this article we attempt to evaluate the usefulness of the medical literature in providing information on the appropriateness of six frequently used medical and surgical procedures.[2,3] We studied the literature through 1981 on carotid endarterectomy, cholecystectomy, upper gastrointestinal endoscopy, colonoscopy, coronary angiography and coronary artery bypass operation.

Methods

We located articles by searching the US National Library of Medicine's computerized bibliographic data base (MEDLINE), by reviewing references in the articles uncovered by the MEDLINE search and in leading textbooks and by analyzing articles suggested by a 15-member advisory group. The results were reviewed by Stanley Cohen, MD, of the Veterans Administration, and Dennis M. Jensen, MD, and Ronald D. Tompkins, MD, of UCLA, Los Angeles. We assigned all publications to one of eight categories: controlled trials in which subjects are randomly assigned to one or more experimental and control groups and all data are collected prospectively; other prospective studies in which subjects are not randomly assigned to groups; retrospective studies in which the investigator defines clearly which existing source of information is used; probably retrospective studies with unspecified or unclear data sources; surveys of opinion and experience; editorials; reviews of research, and textbooks. We excluded case reports and articles on technical advances in doing a procedure. No attempt was made to qualitatively score the quality of journals, articles or their contents. Our concern was with uncovering the available literature's recommendations for the use of each procedure, the frequency of its use with specific groups of patients, the evidence for its efficacy compared with alternative diagnostic or therapeutic strategies, the types and rates of complications from its use and the costs of doing it.

Results

Characteristics of Articles and Textbooks

The six literature reviews uncovered 803 germane publications. Relatively little information was available on carotid endarterectomy or colonoscopy compared with coronary angiography or the coronary artery bypass procedure. Except for that on cholecystectomy, most of the literature appeared after 1975 (Table 1).

On analyzing the content of the 803 publications (Table 2),

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TABLE 1.—*Year of Publication of Articles and Textbooks Included in a Literature Review of the Use of 6 Surgical Procedures*

Procedure	Year of Publication: Before 1970	1970-1975	1976-1981	Number of Publications
Carotid endarterectomy	10	50	88	148
Cholecystectomy	29	31	51	111
Upper gastrointestinal endoscopy	4	29	79	112
Colonoscopy	0	35	57	92
Coronary angiography	8	53	131	192
Coronary artery bypass graft procedure	0	21	127	148
Total*	51(6)	219(27)	533(66)	803(100)

*Number in parentheses indicates percentage of total number of publications.

TABLE 2.—*Content of 803 Publications on 6 Medical and Surgical Procedures*

Procedure	Content: Indications	Population-Based Use*	Efficacy	Complications	Costs
Coronary angiography	31	6	77	33	7
Coronary artery bypass graft procedure	29	7	116	73	6
Carotid endarterectomy	56	0	50	43	0
Upper gastrointestinal endoscopy	53	0	52	38	9
Colonoscopy	50	0	22	54	4
Cholecystectomy	57	32	19	39	5
Total†	276(34)	45(6)	336(42)	280(35)	31(4)

*Refers to use in a defined area such as the residents of a state or county

†Number in parentheses indicates percentage of publications. One publication might contain data on more than one topic and so totals add up to more than 100%

we found that 276 (34%) had information on the indications for using the procedure, 45 (6%) described the use of the procedure in a specified population such as that of a county or state, 336 (42%) reported the procedure's relative efficacy, 280 (35%) had information about the complications resulting from the procedure and 31 (4%) concerned the costs of doing the procedure.

Of 571 research studies—the rest were textbooks, surveys, reviews or editorials—10% reported the results of randomized, controlled trials (Table 3). Most knowledge about the six procedures originated in retrospective or presumably retrospective studies (66%), so it is not surprising that more than three fourths of the data on indications and two thirds of the information on efficacy were found in studies that used a retrospective research design (Table 4).

Indications

We assembled indications from the literature that were specific recommendations for physicians to act clinically. Statements of theoretic interest or concerns regarding the use of a procedure were not included.

We found that the indications for using all six procedures were characterized by disagreement and unanswered questions. For example, whereas many investigators agreed that endoscopy is indicated for patients with acute gastrointestinal bleeding,[4-6] they disagreed on when to do the procedure. Some asserted an early endoscopy was not essential if results of an adequate upper gastrointestinal x-ray study were available[7]; others argued that massively bleeding patients would be at a disadvantage without early endoscopy. The definition of early varied from within 12 hours[8] to no later than 24 hours[9,10] to 48 hours.[11-13]

For colonoscopy, the literature was unclear as to the schedule for colonoscopic follow-up in patients who had a polypectomy[14-16] or a colonic cancer resected.[16,17] Controversy also persisted in the literature on cholecystectomy, particularly whether the procedure should be done for patients with asymptomatic gallstones.[12,13,18]

The indications for the cardiovascular procedures were also characterized by uncertainty. The literature showed agreement that a coronary artery bypass procedure, for example, was indicated for patients with left main coronary artery obstruction or those with angina that does not respond to medical management. For all other clinical situations, we found much disagreement.[19-25]

A review of the indications for carotid endarterectomy also revealed controversy. Relatively strong support existed for the use of the procedure in treating patients who had a combination of classic carotid transient ischemic attacks and a surgically amenable lesion on the side appropriate to the symptoms. But disagreement was plentiful over the use of the procedure in patients who had a completed stroke,[26-29] were asymptomatic[30-33] or had an evolving stroke[34-36]; even the issue of what is meant by surgically amenable stenosis was unresolved.[37-39]

Frequency

No information could be found in the literature that described the use in a specific population (such as residents of a city or region) of fiber-optic colonoscopy, upper gastrointestinal endoscopy or carotid endarterectomy. A few population-based studies could be found for the use of coronary artery bypass graft procedure. These showed that the procedure was frequently used, for example, in the United States—at least 70,000 done in each year studied by the researchers—its use increased for a time, but may have leveled

TABLE 3.—*The Research Methods Used in Published Studies of 6 Medical and Surgical Procedures*

Procedure	Methods*				
	Randomized Controlled Trials	Other Prospective Studies	Retrospective Studies, Clear Data Sources	Probably Retrospective Studies, Unclear Data Sources	Total Number of Research Articles
Carotid endarterectomy	1	17	20	25	63
Cholecystectomy	11	1	77	4	93
Upper gastrointestinal endoscopy for diagnosis	10	20	13	33	74
Colonoscopy	0	6	8	38	52
Coronary angiography	19	55	84	7	163
Coronary artery bypass graft procedure	18	41	62	5	126
Total†	59(10)	140(25)	264(46)	112(20)	571(100)

*See text for definitions.
†Number in parentheses indicates percentage of total number of research articles (571) for all procedures

TABLE 4.—*Relationship of Research Design to Type of Information Produced for 6 Medical or Surgical Procedures*

Research Design*	Type of Information				
	Indications, N=171, No. (%)	Population-Based Use, N=74, No. (%)	Efficacy, N=284, No. (%)	Complications, N=197, No. (%)	Costs, N=16, No (%)
Randomized, controlled trials	13 (8)	0 (0)	59 (21)	17 (9)	1 (6)
Other prospective studies	23 (13)	1 (1)	47 (17)	24 (12)	2 (13)
Retrospective studies, clear sources of data	70 (41)	72 (97)	116 (41)	103 (52)	8 (50)
Probably retrospective studies or unclear data sources	65 (38)	1 (1)	62 (22)	53 (27)	5 (31)

*See text for definitions

off by 1980.[4,40-43] Some US population-based use rates were also available for coronary angiography.[40,44-48] In the United States, this procedure is characterized by a steady growth in use, with the number of angiograms per year estimated to be between 300,000 and 400,000; often they are carried out in facilities whose cardiac catheterization rates are low: fewer than 300 per year. Population-based use rates were also found for cholecystectomy and included rates for different years, geographic regions and patient characteristics.[49-56] In 1980 a cholecystectomy was done on more than 20 persons out of every 10,000 in the United States. The procedure was used twice as often for women as for men. In certain census regions cholecystectomy was done more often than in others, with a ratio of high to low use of 1:3.

Efficacy

The efficacy of a procedure must be assessed by the benefit it confers on patients relative to its risks. The randomized, controlled trial is one accepted way to show a procedure's benefits and risks and to compare them with those of possibly competing techniques.

The efficacy of the coronary artery bypass graft operation was the focus of 11 randomized, controlled trials. Six investigated the efficacy of the procedure for patients with chronic stable angina.[57-62] The researchers concluded that the procedure is effective for those patients in whom angina is inadequately controlled by medical management. It also prolongs life in patients with left main coronary artery stenosis and in some patients with three-vessel disease. Four randomized, controlled trials were done to test the efficacy of a coronary artery bypass graft procedure for patients with unstable angina.[63-66] These studies showed that the incidence of anginal pain is reduced with surgical treatment, but the operation's effect on survival is less certain. Two randomized, controlled trials were done to research the efficacy of a coronary artery bypass graft procedure after an acute myocardial infarction.[58,67] The trials were unable to confirm the operation's effectiveness in prolonging life in myocardial infarction survivors in whom angina did not develop.

Many patient groups on whom a coronary artery bypass procedure could be done were excluded from these studies, however. Very few women or patients older than 65 were included in research on the use of the operation in patients with chronic stable angina. Even fewer patients with ejection fractions under 30% were studied. Patients with severe concomitant illnesses were usually systematically excluded. No randomized, controlled trials of the efficacy of a coronary artery bypass graft operation could be found for patients who were in the acute phase of myocardial infarction; who received a second bypass operation; who survived sudden cardiac death, or who had variant angina, chest pain of uncertain origin or were asymptomatic.

We found just one randomized, controlled trial to evaluate if carotid endarterectomy prevents stroke,[68] and it failed to show the operation's efficacy. The current applicability of the study is uncertain, however, because it was done between 1961 and 1965 and medical and surgical therapies have changed since then. Also, the research concerned patients with a limited number of neurologic presentations.

Eight randomized, controlled trials provided data to support the efficacy of endoscopy for patients with acute upper gastrointestinal bleeding (for instance, Dronfield and co-

workers and Morris and associates[7,69]); only one[70] studied patients who were endoscoped for other reasons, and it confirmed the diagnostic accuracy of the procedure when compared with radiography.

No randomized, controlled trial could be found that compared a surgical approach (either early or delayed) with a conservative medical approach (avoiding surgical treatment unless forced to operate because of a complication) in patients with acute cholecystitis. Four randomized, controlled trials were available,[71-74] however, on the timing of a surgical procedure (early versus delayed) for patients with acute cholecystitis; these supported an early procedure.

No randomized, controlled trials of coronary angiography were available, but a large body of literature compared one or more noninvasive cardiac studies with coronary angiography and, assuming that the angiography provided the correct diagnosis, gave data on the diagnostic accuracy of the noninvasive test. These investigations did not randomly allocate patients to differing diagnostic methods, one of which included angiography, nor did they assess outcomes for clinically homogeneous patient groups. Therefore, we could not assess the implications for the patient's health of using methods other than angiography for the diagnosis of coronary artery disease in patients with specific symptoms such as chest pain of uncertain origin or chronic stable angina.

No randomized, controlled trial was found to study the efficacy of colonoscopy, nor were data from any kind of prospectively done research available for review.

Complications

For all six procedures, data on complications were available primarily from retrospective studies or from physician surveys that tallied complication rates rather than from more rigorous research. The use of surveys probably was dictated by practical necessity. A large number of patients needs to be observed for a researcher to be confident that a low frequency of complication has occurred. The costs of obtaining large samples for prospective research are considerable; surveys and retrospective studies are less expensive. Despite this possible justification, the literature revealed many inadequacies in presenting information on the complications of a procedure.

Research on the complications from endoscopy and colonoscopy basically ceased to be reported after 1977. Because of this, our estimates of the incidence of complications from these procedures may have been inflated; improvements in instrumentation and physicians' experience may have resulted in decreased complication rates.

A more serious problem with the data in the literature on complication rates was the failure of many researchers to describe carefully the symptoms for which they did a procedure. About 98% of the data on the complications from endoscopy, for example, came from surveys of physicians in which the symptoms—including the presence or absence of bleeding—for which the procedure was done were not specified.[75-77] When reviewing the complications of cholecystectomy, we encountered a similar problem. In several articles, the complications for cholecystectomy were described, but the clinical presentations were not.[78-80] As a result, we could not tell if relatively low rates of infection and short hospital stays reported in certain papers accurately reflected good care or if they might have resulted from a preponderance of elective operations or those carried out mainly in relatively healthy, young patients.

Finally, data on complications in most studies of carotid endarterectomy, coronary artery bypass procedure and cholecystectomy came from research that was conducted in major medical centers and teaching hospitals. We could not infer the applicability of the results to the care provided by typical physicians in typical hospitals.

Cost

Few sources of data could be found on the charges or cost of cholecystectomy,[56] coronary artery bypass grafting[43] or coronary angiography,[81] and none were available on carotid endarterectomy. Information on charges or potential savings in the United States from using colonoscopy as opposed to a surgical procedure to remove polyps could only be obtained from four articles published between 1973 and 1975.[82-85] Nine studies (one a randomized, controlled trial) addressed the costs of upper gastrointestinal endoscopy (see, for example, Holdsworth, Merion and Peterson and their colleagues[86-88]).

Discussion

Considered as a whole, the clinical literature is a helpful but not a sufficient source of information on the appropriate uses of these six procedures. The most useful were the results of randomized, controlled trials on carefully selected groups of patients. The research methods and data collection activities in other studies were sometimes unsound or explained poorly. The number of persons who participated in some investigations was often not given, and essential characteristics of patients, such as their symptoms, were also omitted. Additionally, we could not always infer from a researcher's explanation whether a study's design was retrospective or not and even where and how data were gathered.

The information we sought was often unavailable, inconclusive or contradictory. With the exception of cholecystectomy, little could be found on the costs and use of the six procedures. We found scant data on how the cardiac procedures were actually being used and contrary views on the indications for doing a carotid endarterectomy.

We are aware that our work may not contain all that is known about a procedure. We relied on published data, and some researchers may not have reported everything they did or found.[89] Also, we may have failed to uncover some published articles even though we had others check our bibliography for comprehensiveness. Despite these caveats, we have concluded that the patterns of inadequacy in the clinical literature for all six procedures are pervasive.

How might the clinical-epidemiologic approach to cost containment work best when it cannot rely on literature alone? First, vigilance is needed in interpreting the findings of reported research, a stance requiring careful screening of a study's methods. Although it is unrealistic to expect all physicians to become experts in research methods, familiarity with the available standards for conducting and reporting the results of clinical investigations[90,91] unquestionably is desirable. Publication does not automatically guarantee the soundness of a study's finding.[92,93]

Second, clinicians, using their experience, may be able to extrapolate findings that pertain to the appropriateness of a procedure's use in patients who have participated in a randomized, controlled trial or another rigorously done study to

patients who have not. They can also judge the appropriateness of indications for a procedure's use, although unanimity must not be expected. In one study, three separate panels of physicians used a modified Delphi approach[94,95] to evaluate the appropriateness of hundreds of specific indications for coronary angiography, coronary artery bypass graft procedure, carotid endarterectomy, colonoscopy or upper gastrointestinal endoscopy.[96] Although agreement among panelists was enhanced by using a highly structured consensus method, disagreement on appropriateness was found for as many as 30% of the indications. Among the explanations for this relatively high level of disagreement was the scarcity of experimentally derived data about the risks and benefits of a procedure's use.

Clinical researchers can be of great assistance in assuring that health funds are wisely spent. The long-run success of the clinical-epidemiologic approach depends on such researchers targeting their efforts to the need for information revealed by this study of the inadequacies in the literature. If published information were more complete, it might be easier for clinicians to recommend cuts in inappropriate services while fighting to maintain an increased access to the appropriate ones.

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Chemical Contamination of California Drinking Water

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Drinking water contamination by toxic chemicals has become widely recognized as a public health concern since the discovery of 1,2-dibromo-3-chloropropane in California's Central Valley in 1979. Increased monitoring since then has shown that other pesticides and industrial chemicals are present in drinking water. Contaminants of drinking water also include naturally occurring substances such as asbestos and even the by-products of water chlorination. Public water systems, commercially bottled and vended water and mineral water are regulated, and California is also taking measures to prevent water pollution by chemicals through various new laws and programs.

(Russell H, Jackson RJ, Spath DP, et al: Chemical contamination of California drinking water. West J Med 1987 Nov; 147:615-622)

Patients concerned about the health risks of contaminated groundwater may seek advice from their physicians. This review is intended to assist physicians in responding to such questions. It will cover groundwater and surface water contamination and the scientific basis of regulatory standards.

The vulnerability of groundwater to chemical contamination by pesticides was most dramatically revealed by the 1979 discovery of the pesticide 1,2-dibromo-3-chloropropane (DBCP) in the Central Valley of California. Like other soil fumigants, DBCP was injected into the soil to kill nematodes. Since 1955 about 1.4 million kg (3 million lb) of DBCP was being applied annually in California before its use was suspended in 1977 following findings of sterility or reduced sperm counts in male workers at a formulating plant.

In California about 2,500 wells have been found to be contaminated with DBCP; more than half of these wells have been made unusable as a drinking water source because DBCP concentrations exceed the state health advisory guideline (action level) of 1 part per billion (ppb; parts per billion $= \mu g$ per liter).[1(p54)] DBCP has also been found in wells in Arizona, South Carolina, Maryland and Hawaii. Its widespread occurrence and persistence in groundwater—one study estimates its half-life in soil at 141 years[2]—underscore the need for prevention rather than cleanup.

Monitoring for pesticides and industrial chemicals in drinking water has greatly increased in California since 1979. The California State Water Resources Control Board has verified 441 cases of groundwater contamination by 54 different pesticides in 28 counties, not including the DBCP cases.[1(p 66,77)] Many of these incidents may have come from spills or the improper disposal of pesticides rather than from agricultural use.[1(p66)]

No single inventory of industrial chemical groundwater contamination incidents exists, but the results from the sampling of wells of large public water systems prompted by California's AB 1803 program show that 18.3% of the wells had some contamination and 5.6% exceeded one or more state standards.[3] These public water system wells were mostly deep and therefore less likely to be contaminated by pesticides. About 41% of the contaminated wells were in Los Angeles County, which indicates that industrial sources such as storage tanks, improper holding ponds, leaking sewers and even parking lot runoff are major sources of contaminants. Before further discussing water contaminants and their health effects, however, an understanding of standards and regulations will help.

Regulatory Programs and Standards

Under the authority of the Safe Drinking Water Act (PL 93-523), the Environmental Protection Agency (EPA) has had national authority since 1974 over drinking water quality and the regulation of public drinking water systems, but states may create and administer their own safe drinking water programs if they meet minimum EPA standards. The California Safe Drinking Water Act states that water delivered by public water systems in the state shall "be at all times pure, wholesome, and potable."[4]

To ensure drinking water quality, the EPA (or the states) sets standards for contaminants in drinking water, called maximum contaminant levels (MCLs). These standards seek to protect public health while taking into account the economic costs and technologic feasibility of treating or removing the contaminants. MCLs are divided into two categories: primary, for chemicals that have adverse health concerns, and secondary, for those that have mainly aesthetic effects—that is, taste, odor and appearance of the water. MCLs are legally enforceable standards. The EPA has established few MCLs in the past. Until recently, primary MCLs covered only ten inorganic and seven organic chemicals plus radionuclides. Because of the delay at the federal level and unique contamination issues in California, the California Department of Health Services (CDHS) sets certain MCLs of its own.

When contaminants without MCLs are detected in drinking water supplies, the EPA and some states develop nonenforceable health advisory guidelines (called action levels in California). The guidelines help distinguish between hazardous and nonhazardous exposures and prompt water utilities to notify customers and to take corrective measures

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ABBREVIATIONS USED IN TEXT

CDHS = California Department of Health Services
DBCP = 1,2-dibromo-3-chloropropane
EPA = Environmental Protection Agency
MCL = maximum contaminant level
ppb = parts per billion
THM = trihalomethane

when action levels are exceeded. Though public notification of action level excesses used to be voluntary, the CDHS now requires large water suppliers to notify customers whenever action levels or MCLs are exceeded. Recent legislation (AB 1803) requires water suppliers to monitor wells for all chemicals that are used in the area of the aquifer rather than just for chemicals with MCLs, as was previously required. The CDHS is also developing action levels for all new contaminants detected in drinking water systems, as well as evaluating health effects of contaminants found in private wells.[3]

To establish standards, toxicologists consider the data on acute and chronic effects, neurotoxicity, teratogenicity, mutagenicity and carcinogenicity. With noncarcinogenic contaminants, scientists often recommend that the standard be set at a level 10, 100 or even 1,000 times below the "no-observed-adverse-effect" level determined from experiments in animals to include a safety margin or uncertainty factor. This safety factor reflects possible differences between animal species and humans and differences in susceptibility in humans. It may be increased when there are uncertainties in the available toxicologic data, such as when the no-observed-adverse-effect level has not been determined. Exceeding an MCL or action level indicates an encroachment into the margin of safety but does not necessarily indicate an endangerment of public health.

Because of the nature of the carcinogenic process, however, no-observed-adverse-effect levels are generally nonexistent. Carcinogenesis is believed in many cases to involve the interaction of a carcinogen with DNA or other target macromolecules, and cancer can ensue from this event within a single cell.[5,6] Regulatory agencies, therefore, generally consider carcinogenesis to be a nonthreshold process.

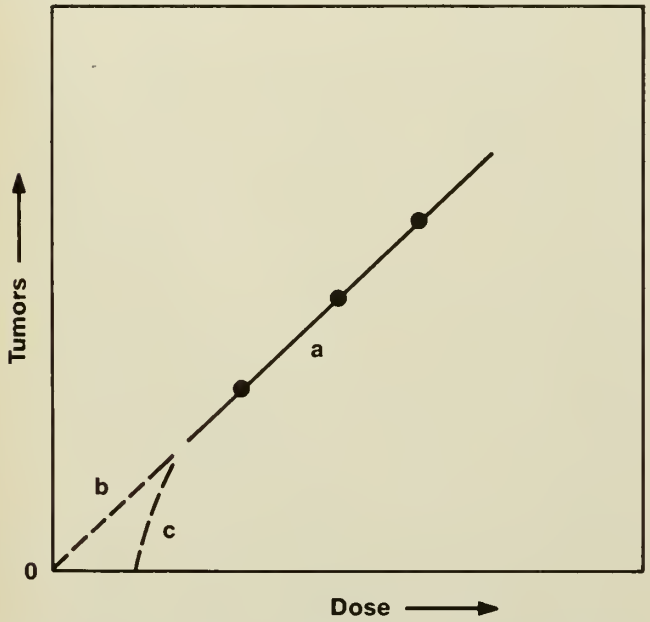

Figure 1.—The concept of threshold versus no threshold is shown by the extension of line **a** to 0 dose: solid line **a** is an experimentally determined dose response from high doses, dashed line **b** is a downward extrapolation showing a nonthreshold effect using the one-hit model of carcinogenesis and dashed line **c** shows a threshold effect (modified from Van Duuren and Banerjee[7(p87)]).

Mathematical models are used to assess cancer risks. Because only 100 or fewer treated animals per sex per species are usually used in experiments, the doses must be high enough to produce statistically meaningful results but not so great as to produce adverse effects other than tumors, such as toxicity or low weight gain. From the data points at the high experimental doses, a curve is extrapolated downward to estimate what effects would occur at the very low doses found in environmental exposures. Using high doses to determine effects of chemicals that normally exist at very low levels in the environment is controversial.

Figure 1 shows the difference between the threshold and nonthreshold models.[7] The curve on the graph is simply for illustration; more complex functions are used in extrapolating low-dose effects.[5] The National Research Council's Board on Toxicology and Environmental Health Hazards recommends that "as a general rule, nonthreshold models should be used" for carcinogens except when evidence from animal experiments shows otherwise.[8]

Setting Standards for Carcinogens

Whenever feasible, standards and action levels for carcinogens are established as "acceptable" or *de minimis* risk. The EPA has established the upper limits of acceptable risks between one additional case of cancer in a population of 100,000 to one in 1 million (10^{-5} to 10^{-6}) over a 70-year lifetime.[9] Similarly, the CDHS considers risks at the one-in-a-million level or below to be negligible. This risk level is intended to be health conservative because it involves involuntary risk. Public health officials believe that although society willingly accepts much higher voluntary risks, it will not tolerate similar risks for someone else's economic benefit.

One risk assessment study of the drinking water in 25 cities has noted that contaminants in drinking water are usually present in mixtures and that the aggregate risks from these mixtures in most of the cities studied "are comparable to other risks that society puts up with but tries to control."[10] In drinking water found to have a high aggregate risk, such as 2.5 persons per 1,000, most of the risk was due to the presence of the by-products of chlorination.

Another approach to determining the health effects of contaminants in water is through epidemiology, but only a few studies have been done of synthetic organic chemicals in drinking water. Nearly all of these investigations have been on cancer risk and most have been aggregate-risk studies in which geographic areas are the units of observation rather than people.[11] Aggregate studies can be done more rapidly because public data sources usually provide the necessary information on cancer mortality, but inherent problems such as variations in individual exposure within an area and potential confounders make inferences of causation difficult. Shy concluded that although aggregate studies can be useful in justifying more costly epidemiologic investigations of exposed persons, large case-control interview studies are needed to clarify causal relationships.[11] One such study, as noted later, has been conducted in Santa Clara County by the CDHS, and another has been carried out in Woburn, Massachusetts, where an excess prevalence of childhood leukemia has been investigated.

Pollution Implications

Drinking water action levels are not set as limits for pollution—that is, as permits for contamination up to the health-based level. Drinking water standards indicate when contamination levels in drinking water have reached such an unacceptable level that alternate water sources should be considered or the water treated to protect human health. Action levels do not reflect environmental bioaccumulation in plants and animals, the fate and toxicity of chemical degradation products or human exposure to the interaction of complex chemical mixtures in various media. The federal Clean Water Act and state laws deal with protecting water from pollution.

Agricultural Contaminants

Fumigants

DBCP is the most widespread pesticide contaminant in groundwater in California and the United States. Many wells in California's Central Valley have been contaminated with DBCP concentrations above the California action level of 1 ppb. DBCP is known to cause sterility in exposed workers and testicular atrophy in test animals and may be a carcinogen for humans as well.[12,13] California's action level, established in 1979, was based on the limitations of the laboratory analytic methods at that time. This level will probably be lowered considerably when California establishes a maximal contaminant level for DBCP. The CDHS has estimated the lifetime risk from consuming 1 ppb of DBCP to be 670 additional cases per million exposed population.[14]

In 1982 the CDHS, using census tracts, did a descriptive epidemiologic study of selected cancer mortality compared to DBCP drinking water contamination levels in Fresno County for 1970-1979. The study noted statistically significant trends of increasing stomach cancer and lymphoid leukemia with increased DBCP levels in water.[15] The conclusion was that mortality data alone, as used in this study, could not be relied on to implicate DBCP in drinking water as a cause of cancer, and it was suggested that further studies be done in which the data could be better controlled to separate out the confounding factors such as socioeconomic status and ethnicity.

After DBCP was suspended from use in 1979, the use of other fumigants increased, and now most have also been detected in wells, including 1,2-dichloropropane, 1,3-dichloropropene and ethylene dibromide (Table 1). The California Department of Food and Agriculture is seeking to limit the 1,2-dichloropropane content of Telone—the one product remaining on the market that contains it—from its present 35% level to only 0.5%. Action was taken to suspend the use of ethylene dibromide as a fumigant in California when it was detected in groundwater and in grain products in 1984. Because ethylene dibromide is so potent a carcinogen in animals, the CDHS maintains that any confirmed findings of the chemical in wells at or above the California action level of 20 parts per trillion (or nanograms per liter), the current detection limit, warrant recommending the use of alternate sources of drinking water.[16,17]

The main fumigant now in use is methyl bromide,[18] which is also under investigation for carcinogenicity.[19] Methyl bromide is often used in combination with chloropicrin. If methyl bromide and other chemical fumigants are found unacceptable due to adverse effects on health and the environment, there will be few registered alternative chemicals left for controlling nematodes.

Herbicides

Herbicides, the most heavily used of agricultural pesticides, have polluted surface water and groundwater. Rice herbicides, for example, have contaminated the Sacramento River, which serves as a drinking water source for Sacramento. Complaints about a bitter taste in the city water were correlated with the detection of the herbicides thiobencarb

TABLE 1.—*Agricultural Chemicals*

Chemical	*Use*	*MCL or Action Level*	*Main Health Effects*	*Status*
1,2-Dibromo-3-chloropropane	Soil fumigant nematocide	1.0 ppb, Calif; 0.02 ppb, Hawaii (detection level)	Suspected human carcinogen, sterility in more highly exposed men	Suspended 1977—California, banned 1979
1,2-Dichloropropane (1,2-D)	Soil fumigant nematocide	10 ppb, Calif	1,2-D and 1,3-D are components of D-D and Telone; cancer bioassay of commercial mixture in rats and mice positive*	Shell has withdrawn D-D formula nematocide; state seeks to limit 1,2-D in nematocides to 0.5% (from 35% now)
1,3-Dichloropropene (1,3-D)	Soil fumigant nematocide	None set		
Ethylene dibromide	Soil fumigant nematocide	20 ppt (detection limit)	Potent animal carcinogen; suspected human carcinogen†	Banned as fumigant; water consumption inadvisable if detected
Methyl bromide; chloropicrin	Soil fumigant nematocide	None set	Methyl bromide undergoing carcinogenicity testing; chloropicrin (tear gas) is acutely toxic	Often used together; these are main fumigants in use now
Molinate (Ordram)	Rice herbicide	20 ppb	Low acute toxicity	Detected in Sacramento, Calif, city water
Thiobencarb (Bolero)	Rice herbicide	10 ppb (health), 1 ppb (taste)	Low acute toxicity	Detected in Sacramento, Calif, city water
Bentazon (Basagran)	Herbicide	8 ppb	Low acute toxicity; other effects under evaluation	Detected in Sacramento, Calif, city water
Simazine	Herbicide	150 ppb	Low acute toxicity	Found in some water systems
Atrazine	Herbicide	15 ppb	Low acute toxicity	Found in some water systems
Nitrate	Fertilizer waste product	45 ppm	Methemoglobinemia in infants	Problem in some agricultural areas

MCL=maximum contaminant level, ppb=parts per billion, ppm=parts per million, ppt=parts per trillion

*From the National Toxicology Program, US Dept of Health and Human Services.[16]
†From report to California Air Resources Board, 1984.[17]

(Bolero) and molinate (Ordram) in the city's water.[20,21] Because the consumer complaint and sampling data show the taste detection limit for thiobencarb to be about 1 ppb, the CDHS took the unusual step of setting a secondary action level of 1 ppb for thiobencarb, ten times below the primary health protection level, to prevent aesthetic degradation of the drinking water. Another herbicide more recently detected in the Sacramento River is bentazon (Basagran), for which the CDHS has set an action level of 8 ppb.[22] Controls on herbicide use have resulted in reducing the herbicide levels in the city's water and general compliance with the action levels.[23]

Herbicides that have been detected in groundwater include simazine, atrazine, bromacil, prometon and diuron.[24] Action levels have been established for the first two of these. None of these herbicides have been found at concentrations that cause health concerns.

Nitrate

Nitrate is California's major groundwater pollutant. It enters the water supply through nitrogen-containing fertilizers, feedlot wastes and failed septic systems. A 1983 survey of small water systems in California found 238 violations of the 45 ppm maximum contaminant level (ppm = mg per liter), with levels ranging up to 228 ppm.[25] At high levels, nitrate through conversion in the gut to nitrite can cause methemoglobinemia, a hazard to infants younger than 6 months.[26] The CDHS advises that bottled water be used in preparing infant formula whenever the nitrate levels in drinking water are found to exceed the MCL. Boiling is not effective for removing nitrate or other nonvolatile substances from water.

In an epidemiologic study, a possible association was found between nitrate in drinking water and neural tube defects in infants in South Australia, but there is no evidence for a cause and effect relationship.[27] Studies in animals do not suggest that nitrate is a teratogen; further studies are needed, however, for other reproductive effects using updated protocols. Likewise, carcinogenicity data are inconclusive. Some epidemiologic studies have correlated an increased exposure to nitrate or nitrite in the diet or drinking water with an increased prevalence of stomach cancer, but again a causal relationship is lacking. Nitrate conversion in the human stomach to *N*-nitroso compounds, some of which are highly carcinogenic, is known to be possible, but there is no evidence to conclude that nitrates or nitrites themselves are carcinogenic, and data are inadequate to determine the biologic significance of such possible exposure to *N*-nitroso compounds.

Industrial Contaminants

Volatile synthetic organic chemicals have been widely detected in groundwater. Their uses include cleaning jet engines on military bases and decontaminating microchips in the electronics industry. The EPA has selected them as the first group of chemicals for which it is developing MCLs.[28]

Four such volatile organic chemicals most commonly found in California drinking water systems are tetrachloroethylene or perchloroethylene, trichloroethylene, 1,1,1-trichloroethane and vinylidene chloride or 1,1-dichloroethylene (Table 2).[3] Except for vinylidene chloride, a monomer used in manufacturing plastics, these are industrial solvents. Officials are concerned that some of the volatile organic chemicals cause cancer, but data on this and reproductive effects are mainly from animal studies; data from human studies are limited. Many solvents are able to cross the placenta. One

TABLE 2.—*Industrial and Other Contaminants in Drinking Water*

Chemical Name	*Use*	*MCL or Action Level*	*Health Concern*	*Status*
Trichloroethane	Industrial solvent	200 ppb, Calif action level; proposed US MCL, 200 ppb	Carcinogen in one mouse study, not in four other studies; no evidence in exposed workers; data inadequate to assess; no significant effects but showed delayed development that was reversible*†	Common contaminant in groundwater
Trichloroethylene	Industrial solvent	5 ppb, Calif action level; proposed US MCL, 5 ppb	Probable human carcinogen with low potency; no teratogenicity in animal studies‡	Common contaminant in groundwater
Tetrachloroethylene (1,1-dichloroethylene)	Industrial solvent	4 ppb action level	Carcinogen in mice and rats; some evidence in exposed workers; no teratogenicity; possible fetotoxicity at high dose§	Common contaminant in groundwater
Vinylidene chloride	Plastics manufacture	6 ppb action level	Evidence of carcinogenicity equivocal; weak, if at all‖	Common contaminant in groundwater
Total trihalomethanes	Water disinfectant by-product	100 ppb MCL	Cancer	Under review by EPA
Fluoride	Naturally occurring element	1.4 to 2.4 ppm, Calif; 4 ppm US	Teeth mottling, skeletal fluorosis	Recent change in US MCL under legal challenge
Asbestos	Naturally occurring element	None	Cancer	Widespread in drinking water systems
Arsenic	Naturally occurring element	5 ppb MCL	Cancer	Elevated in some mineral waters
Selenium	Naturally occurring element	10 ppb MCL	Causes deformities in avian and livestock offspring; high levels in humans cause gastrointestinal problems, hair and nail loss	Main concern is environmental contamination

EPA=environmental Protection Agency, MCL=maximum contaminant level, ppb=parts per billion, ppm=parts per million

*From Epidemiological Studies and Surveillance Section, California Department of Health Services.[30]
†From Schwetz et al [31]
‡From Environmental Criteria and Assessment Office, US Environmental Protection Agency.[32]
§From the National Toxicology Program, US Department of Health and Human Services.[33]
‖From the Community Toxicology Unit, California Department of Health Services.[34]

case of hepatic toxicity in a newborn with exposure to perchloroethylene through human milk has been recorded.[29]

One highly publicized solvent contamination episode in California involved the leak of an estimated 50,000 gallons of mixed solvents, mostly 1,1,1-trichloroethane, from an underground waste storage tank at the Fairchild Camera and Instrument Company in San Jose, California. A well serving a nearby residential community had been contaminated when the leak was discovered in 1981. Residents became concerned over an apparent excess of birth defects in their neighborhood, and the CDHS, at the request of the Santa Clara County Health Department, agreed to conduct an epidemiologic investigation.[30-34]

The CDHS studies released in January 1985 showed that combined birth defects in a census tract served by the contaminated well were about three times higher than in a comparison area and spontaneous abortions were about two times higher. Major cardiac defects in the entire area served by the water company were about 2½ times the county average. The studies, however, were inconclusive because the timing and distribution of these outcomes made the contamination of the water unlikely to have been the cause of the health outcomes. For example, the cluster of cardiac defects was seen extending outside the boundaries of the distribution system of the water company with the contaminated well. Also, available toxicologic data indicate that 1,1,1,-trichloroethane is not teratogenic. Moreover, the studies found that the pattern of congenital malformations "is not one that is common for a single teratogen since no specific congenital malformation was responsible for the excess."[30]

Fairchild has settled a multimillion dollar citizens' lawsuit but did not admit guilt. CDHS is continuing further studies. The EPA is also conducting an integrated environmental management project in Santa Clara County with various agencies to examine health risks from contaminants in outdoor air, surface water and groundwater.[35] Preliminary findings indicate that pollutant levels in the Santa Clara Valley are typical of many other urban areas, and the EPA predicts that "under pessimistic assumptions, contamination of groundwater supplies of drinking water could result in one additional case of cancer every 30 years."[35]

Santa Clara County was one of the first governmental agencies to pass an ordinance requiring water pollution safeguards on underground storage tanks. Many old fuel storage tanks are believed to be leaking, and the state and federal governments are now taking steps to protect against leakage from such tanks.[36]

Other areas with significant groundwater contamination in California are the San Gabriel and San Fernando Valleys near Los Angeles, several military bases in the Central Valley and the Aerojet rocket fuel manufacturing facility near Sacramento.

Naturally Occurring Contaminants

While synthetic or industrial substances have received the most publicity, some naturally occurring substances in water also pose a toxicologic concern. These include asbestos, selenium, fluoride and arsenic (Table 2). Arsenic has been a problem mainly in mineral water.

Asbestos

Asbestos comes mainly from serpentine rock, which is found widely in California's coastal ranges and foothills.[37] Most asbestos settles out in reservoirs or is removed in water treatment plants,[38] but an EPA survey of urban water systems in 365 cities found 41 with asbestos concentrations greater than 10 million fibers per liter.

Studies of cancer in animals ingesting asbestos and epidemiologic studies of populations exposed to drinking water with high levels of asbestos have all been negative. The epidemiologic studies were flawed, however, and a National Research Council committee has found that on reanalysis they produce a relative risk similar to one calculated for gastrointestinal tract cancer based on an occupational exposure to asbestos. The committee estimated that the concentration in water needed to cause a one-in-a-million added lifetime risk of cancer would be a little more than 1 million fibers per liter. Some San Francisco Bay Area water systems have more than 100 million fibers per liter of asbestos.[39]

Selenium

Selenium has been linked with deformities and death in chicks of aquatic birds at the Kesterson National Wildlife Refuge (Central Valley, California) where irrigation discharge water had been stored. Selenium, which derives from marine shales, has been found in few large water systems in the state, but a 1983 survey of small California water systems showed 27 violations of the 10-ppb action level, mostly associated with outcroppings of selenium-rich rock.[25]

Selenium has an extremely narrow therapeutic index: either excess or absence of selenium in the diet causes harm. Because of observed reproductive effects in birds and livestock, the teratogenic potential in humans is of obvious concern, but to date no standard assay for this effect of selenium compounds has been carried out. Selenium has not been determined to be carcinogenic.

The CDHS did a health survey among residents in the Kesterson area matched by age and sex with a control population. Results did not show any trend of adverse health effects.[40]

Fluoride

Fluoride has great public health benefit in preventing dental caries at dosages of 0.5 to 0.7 ppm in water.[41] The fluoride standard is in controversy, however, because in early 1986 the EPA, as part of a settlement of a lawsuit brought by South Carolina, increased the primary drinking water standard from between 1.4 and 2.4 ppm to 4 ppm to protect against skeletal fluorosis and to set a secondary optional standard of 2 ppm to protect against objectionable dental fluorosis.[42] South Carolina, which wanted to avoid the high cost of removing fluoride from groundwater, initially asked that the MCL be changed to 8 ppm. California has not raised its MCL as dental mottling would occur in almost all children exposed to 4 ppm during tooth development, and because skeletal fluorosis has been observed when drinking water containing only 3 ppm is used (skeletal fluorosis becomes crippling when water levels reach 20 to 40 ppm).[43]

Contamination From Water Disinfection and Delivery Systems

Trihalomethanes

The most common synthetic organic chemicals found in US drinking water are by-products introduced during drinking water treatment to prevent infectious disease. Trihalomethanes (THMs) are produced when chlorine reacts with

natural organic materials in the water. Of these chemicals, chloroform (trichloromethane), a known animal carcinogen, is the most common.[44 (p 68626)] Others are bromoform, bromodichloromethane and chlorodibromomethane. In states, including California, that only require disinfection of surface water used for drinking, THMs are seldom found in drinking water from underground sources, but a 1986 amendment to the Safe Drinking Water Act requires that all water be disinfected at the source.[45]

The EPA finds the available epidemiologic evidence for the cancer hazard of THMs in water inconclusive but "at least suggestive of a health risk,"[45] and the National Academy of Sciences in a review of 13 preliminary studies concluded that "the risks were small but that important confounding factors could not be distinguished in indirect ecological studies to allow a precise evaluation of the contributions from THMs."[44 (p 68627)]

The establishment of an MCL of 100 ppb (0.1 ppm) per liter for total trihalomethanes represents an attempt to balance the risks of cancer against the known benefits of preventing infectious disease transmission. Chlorine is considered the most effective water disinfectant because of its reactivity and its residual effect in the water distribution system. Its efficacy has been proved over many years. The EPA has calculated a risk of about 1 additional case of cancer per 2,500 persons with exposure for a lifetime—or 200 additional cases of cancer per 1 million persons with exposure—to the total THMs at the maximum contaminant level based on the extrapolated chloroform risk.[44 (p 68704)]

Chloramines are the main alternative water disinfectant used. Chloramines produce fewer THMs, but they are less effective than chlorine. They must be removed from water at kidney dialysis facilities because they can damage erythrocytes. Chlorine dioxide and ozone are other disinfectants, and all of these disinfectants are oxidants and have the potential to form undesirable by-products, the effects of some of which are just being realized.[46]

Trihalomethanes in treated water represent a higher cancer risk than most toxic pollutants at the levels that the latter have been measured in drinking water. The long-term health effects of all the disinfectants have been in question for some time, and the EPA is reexamining them. Trihalomethane levels can be reduced by using carbon treatment either before chlorination to remove organic matter or after to remove the THMs themselves, but this is costly.

Lead

High levels of lead in water pose a significant hazard to the public, especially to children, who are highly susceptible to its hematologic, renal and neurologic effects. The MCL for lead is 50 ppb, but concentrations in delivery systems are usually less than 10 ppb.[47]

Lead solder used in water distribution lines and occasionally lead pipes and lead-lined storage tanks are the main sources of lead in drinking water. Lead concentration is strongly affected by water pH and hardness as well as by water temperature and the length of time the water sits in the pipes.

No lead concentrations exceeding the EPA drinking water standard have been reported in any main distribution line of California municipal water supplies. Because lead pipes were installed in some California homes in the early 1900s, however, levels exceeding the MCL by several times have occurred in tap water as a result of lead leaching from the pipes and solder.[48]

Concern over the possible subtle neuropsychological effects in children from low-level lead exposure has resulted in new federal and state legislation.[49,50] These laws prohibit using lead solder or flux exceeding 0.2% lead in new installations and repairs or using pipes containing more than 8% lead beginning in June 1988, and they require public water supply systems to notify customers of lead contamination that may cause potential health effects. Notification may be required because of the high corrosivity of water or other factors independent of MCL violations.

Commercially Bottled Water, Mineral Water, Machine Vended Water and Home Treatment Units

Commercially Bottled and Machine-Vended Water

Commercially bottled drinking water and machine-vended water must meet the same standards as tap water. Bottled-water producers use a variety of sources for their product, such as springs, wells and public water systems. Bottled or machine-vended water is usually processed in one of three ways: distillation, deionization and reverse osmosis. Water vending machines usually use water from public drinking water systems but treat the water with carbon filtration to remove organic chemicals, chlorine and other organic tastes or odors. The effectiveness of these processes for removing organic chemicals and minerals varies considerably.

Mineral Water

Mineral water is defined as water containing more than 500 ppm of dissolved solids. It has been exempt from drinking water standards because the minerals are naturally part of the product and because it has not been consumed in high volume due to its taste and high cost. Mineral water quality has historically been regulated by licensing of bottlers on a case-by-case basis, though this may change because of mineral water's growing popularity, especially with its new appeal to the young as an alternative to soft drinks and alcoholic beverages.

Home Water Treatment Units

Concern over drinking water contamination has led to inquiries about devices to treat drinking water in the home. Until 1986 home water treatment units were not regulated for chemical contaminant removal, but two new California laws prohibit false or misleading advertising and require the adoption of performance standards.[51,52] The EPA has also proposed regulations if such units are to be considered an acceptable alternative to central water treatment.[53] Reverse osmosis, carbon filtration and other methods may be used in home treatment units, but their effectiveness in removing different contaminants varies.[53 (pp 46915-46916) -55]

Home water treatment devices have been used in California for many years to remove dissolved solids from the water (for mainly aesthetic purposes). Some of the devices are now being promoted for removing organic chemicals. The Public Water Supply Branch of the CDHS has not encouraged this latter use because drinking water delivered by public water systems already meets (with rare exceptions) state standards or action levels for organic chemicals; there is no program to maintain the units other than an owner's service agreement with the supplier (for example, if the filter breaks

on a reverse osmosis unit, the owner would be unaware of the failure) and secondary problems are inherent in some of these devices, such as bacterial growth on activated carbon filters.

Preventing Water Contamination

Laws have been passed and programs implemented to prevent further toxicant contamination of drinking water. The EPA and California have started programs to monitor underground fuel storage tanks at automotive service stations and other locations. New tanks will have to be double lined and leaking ones replaced. The EPA estimates that 35% of underground fuel tanks leak.[36]

California law prevents the dumping of hazardous wastes near underground aquifers that may be used as a drinking water source. The California Department of Food and Agriculture and the EPA are obtaining data on the fate of pesticide ingredients in the environment to determine their potential to contaminate groundwater. These data will be used to develop use restrictions in areas where pesticides are likely to pollute groundwater. Also, the new requirement (AB 1803) for small water systems in California to be monitored for chemical contaminants will have an effect on detecting problems at an earlier stage. The EPA has a program for protecting groundwater, but it has been criticized by some as "a regulatory patchwork" and inadequate.[56] The EPA soon plans a pilot survey of pesticides in drinking water wells.

Assistance for Physicians

When patients have had exposure to contaminated drinking water, their physicians will need to know the substances involved and their concentration levels to be able to advise the patients about possible health outcomes. Local water purveyors should have information about any contaminants in their systems, and local or state health agencies should be able to give information on water standards or how to analyze well water. The CDHS is producing a series of fact sheets on water contaminants and other reviews on toxic issues (for more information, write to the Community Toxicology Unit, Department of Health Services, 2151 Berkeley Way, Berkeley, CA 94704 and request a publication order form). The Toxic-Info Center, which is operated by the San Francisco Regional Poison Control Center, will answer inquiries from California health and emergency professionals and from the public about the toxicity and hazardous properties of chemicals. The center has a toll-free hotline in California (800-233-3360). A new booklet for persons concerned about drinking water in their communities is "Drinking Water—A Community Action Guide," published by Concern, Inc, 1794 Columbia Road NW, Washington, DC 20009. The CDHS is planning a similar booklet written from a California perspective.

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Book Review

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Ultrastructural Appearances of Tumors—Diagnosis and Classification of Human Neoplasia by Electron Microscopy

Douglas W. Henderson, MB, BS, FRCPA, Director of Electron Microscopy, Flinders Medical Centre, Adelaide, and Honorary Consultant in Ultrastructural Pathology, The Queen Elizabeth Hospital, Woodville, South Australia; John M. Papadimitriou, BA, MD, PhD, MRCPath, FRCPA, Associate Professor of Pathology, The University of Western Australia, and Consultant in Pathology, Royal Perth Hospital and Queen Elizabeth II Medical Centre, Perth, Western Australia, and Mark Coleman, MB, BS, FRCPA, Senior Staff Specialist in Pathology, Flinders Medical Centre, Adelaide, South Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 425 pages, $136.

As with its first edition counterpart, this second edition will prove to be an indispensable addition to the library of anyone involved in the ultrastructural diagnosis of tumors. The authors have done a Herculean task in bringing order to what is often a diffuse and nebulous subject. In organizing the chapter material into organ specific and tumor specific categories, a semblance of order and logic is added to the subject of electron microscopy. Much new material is added on specific organs and tumors not covered in the first edition. Not only are the more common neoplasms included, but the depth of this text is evident to the point that unusual entities such as "anemone" cells and Merkel cell tumor are discussed. A great strength of this text is the ample use of high-quality illustrations. The numerous tables also give fingertip availability of the features of specific tumors as well as a comparison between different tumors. The material is current and the references, numerous. The book is not cheap; however, there is little doubt that it is worth every penny and that it will be invaluable to anyone using the ultrastructural features of tumors as a diagnostic tool.

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First Case

HENRY SCHNEIDERMAN, MD, *Farmington, Connecticut*

This is a tale about fear. The fear, irrational and overpowering, that is currently focused on one sexually transmissible viral infection whose name everybody knows, will surely recur with every deadly new disease. And so throughout this piece the menacing new clinical entity is given the generic name of It, for I believe the human issues remain the same even when the disease changes.

Several patients with It had passed through our hospital and a couple had died, but there was yet to be an autopsy of It. Despite membership on the Infection Control Committee and all the scientific papers saying It was hard to catch even after an inadvertent needlestick, I was afraid. I had consulted Barbara Sanchez, the Infection Control Nurse Practitioner. She had never realized, before seeing a regular cancer autopsy on our invitation the day before, that *liters* of infective material are handled every time. Consequently, we were planning the next step, a "dress rehearsal autopsy of It" for the next week.

That morning I called our secretary and asked, "What have we got?" I almost fell over when she answered, "There's a case of It." On the way to the hospital I hoped, "Maybe Jack is pulling my leg by contriving the dreaded scenario," adding, "If not, this is what we are waiting for. Might as well get it over with," as though I believed myself.

Thank goodness it was my week for autopsy service. Jim Stanton would have been scared to death. George Perez would have considered that he had fulfilled the attending pathologist's role by berating the resident through the closed autopsy room door and then imperiously ordering him to be careful as he walked away. Tom Smith, misguided soul, would have thought he remembered reading something in *People* magazine about pancreatic abnormalities in It and would have meticulously dissected the retroperitoneum, nicking himself and forgetting to remove the lungs along the way.

On arriving at the hospital I learned that the case was real, all right. The young man who had died was my age and distressingly similar to me in professional development.

Instead of the losers, I had Jack, who could "dien" (assist at autopsy) better than anybody when he wanted to; and Aram, one of those residents who counter our fears that the next generation is unprofessional. We were joined by Lenny, the medical student who said yes. Harvey, the one who said no, stood duty outside within earshot because we did not have an intercom. Barbara, bless her calm competence and practicality, came and stayed to watch and advise.

In the 40% of my time allotted to internal medicine, I had examined several patients with It and had come to care about some of them personally. As I prepared to direct the assembled team, I was fighting desperation and the fear that It knew an undiscovered route to the unborn baby in my wife's belly.

We cleared the room and prepared ten big buckets of formalin. We suited up for Mars, tenser than we could admit, and Harvey snapped our picture, with Jack's suit marked "NASA: Captain Nikopoulos" by a wag of a histotechnician.

The two ground rules were "Only one person handles a blade at a time" and "Speak before you move." We brought out the body and examined the surface. I changed gloves. Lenny made notes, one sheet about this case and the other recording Barbara's and my comments for the creation of an "It-autopsy" protocol. Aram watched, eager to touch and in good control of himself. Nothing like this had happened during his earlier training in Cleveland, and this first month at our place had been crammed with new challenges. Jack did the primary incision, smooth as silk, all-star, slow and easy, like this was the hundredth time. We made cultures. I yelled "Stop!" when Jack started to eject the extra blood from the syringe, "Drop it into the disinfectant now. Now! Now!" Lenny changed our masks. They completed the evisceration: the organ block was out. Barbara noticed a blood drip and cleaned it up. Rock-and-roll music played on the radio. This time I was not about to cross Jack by shutting that noise off.

Aram weighed, measured and separated organs into large subunits, doing only a quarter of the usual dissection to minimize the risk of an injury. Each subunit went into fixative, with detailed work reserved for a time after any microbes—the causative agent, the expected enteric protozoans, unsuspected acid-fast bacilli, mounds of cytomegalovirus—would *have* to have died. We changed masks. Lenny wrote down the observations on brain removal. Barbara detailed four more ways we could proceed better, for Lenny's list and for the protocol. Aram changed gloves for the sixth time, Jack for the seventh and I, putatively just an observer, for the third. The last tissue and fluid specimens were taken. We cleaned the body surface yet again and put the body in the tray and then in the bag, and then in the second bag, and then in the third bag for the undertaker, who arrived soon after. A technician, professional and supportive, tried to help by letting him in to the body storage area, and I yelled out for her to detain him, though it meant she would be sore at me.

Finally Aram put the last tissue specimen in a bottle. The knives were soaking in disinfectant, and more disinfectant

(Schneiderman H: First case. West J Med 1987 Nov; 147:623-624)

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was dispensed to wipe down everything. We were done. Nobody had gotten cut. We all complimented each other on commitment and integrity. Harvey took a relaxed "After" picture. We changed. We washed—about five times. It was lunchtime. When we got outside, glorious July sunshine filled the outdoors. Each of us was euphoric, and we had become a team in a way I had never, in ten years' exposure, seen before. I took them all out for drinks at the end of the day, wanting to make some gesture. We all felt it. We feel it still.

The shadow of death, of the poor patient's death and of our own deaths, had passed over us, and we were spared, alive, uninfected. We could do it again. We could do anything. It was not going to get us, physically or mentally. We were so ahead of It that we could do right, in this last service, by someone It had struck down. Hosanna.

In a tiny battle of the big war, we had beaten It. There was hope for us and, a long way off, hope that It, too, would be sent cringing into history.

Postscript. Unfortunately for all the victims, we did have to do it again—seven more times in the next seven months. My beloved son Joseph was born healthy, of course, later that year, and is thriving.

Book Review

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Endourology

Edited by Culley C. Carson, MD, Associate Professor of Urology, and N. Reed Dunnick, MD, Professor of Radiology and Chief, Sections of Uroradiology and Vascular/Interventional Radiology, Duke University Medical Center, Durham, North Carolina. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 315 pages, $58.

Over the past decade, endourology has emerged as a new subspecialty within urology. Radiologists have participated along with urologists, and progress has been rapid. Imaging methods have improved enormously, and new instruments and techniques have been developed at a rapid pace. This field will continue to grow, and the potential to investigate and intervene in the upper urinary system without making a surgical incision will be expanded. Endourology has already changed the pattern of practice for the urologist and the training programs for urology residents.

Carson and Dunnick have compiled an excellent volume using twenty contributors—both urologists and radiologists. Some repetition is inevitable with multiple authors, but everything is here. Techniques are thoroughly and capably described. Discussions are thoughtful, and there are abundant high-quality drawings and radiographs. This volume is recommended to urologists and radiologists and will be particularly beneficial for the resident in training in these two disciplines.

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Chairman, Division of Urology
University of Utah School of Medicine
Salt Lake City

A step up in convenience...
for your hypertensive patients already controlled on doses of labetalol and hydrochlorothiazide
☐ Simplifies therapy with a single tablet per dose
☐ May enhance compliance and reduce medication errors
Glaxo
NEW TRANDATE® HCT
(labetalol HCl and hydrochlorothiazide/Glaxo)
100/25mg, 200/25mg tablets
See next page for Brief Summary of Prescribing Information, including a complete discussion of adverse reactions.
Glaxo
TTZ004 September 1987

TRANDATE® HCT **BRIEF SUMMARY**
(labetalol hydrochloride/hydrochlorothiazide)
Tablets

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® HCT Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® HCT Tablets are indicated in the management of hypertension.

THIS FIXED COMBINATION DRUG IS NOT INDICATED FOR INITIAL THERAPY OF HYPERTENSION. IF THE FIXED COMBINATION REPRESENTS THE DOSE TITRATED TO AN INDIVIDUAL PATIENT'S NEEDS, IT MAY BE MORE CONVENIENT THAN THE SEPARATE COMPONENTS.

CONTRAINDICATIONS: TRANDATE® HCT Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Labetalol HCl: *Cardiac Failure:* Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE HCT therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE HCT Tablets, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, labetalol therapy should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE HCT therapy abruptly in patients being treated for hypertension.

Bronchospastic Disease: Patients with bronchospastic disease should, in general, not receive antihypertensive drugs possessing beta-blocking properties. Because of labetalol's alpha$_1$-blockade and beta$_2$-agonist actions on airway smooth muscle, however, it may be used with caution in patients who cannot tolerate other antihypertensive treatment. If is nevertheless prudent, if labetalol is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia, it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic-blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Diabetes mellitus that has been latent may become manifest during thiazide therapy.

PRECAUTIONS: General: ***Labetalol HCl: Impaired Hepatic Function:*** Labetalol HCl should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). If is therefore recommended that treatment with labetalol HCl be discontinued (see **WARNINGS**) should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Hydrochlorothiazide: Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively, having diarrhea, or receiving parenteral fluids. Thiazides may cause hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, and changes in serum and urine calcium. All patients receiving thiazide therapy should be observed for the clinical warning signs of fluid or electrolyte imbalance, irrespective of cause, which are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscular pains, cramps, or fatigue, hypotension, oliguria, tachycardia; and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, during concomitant use of corticosteroids or ACTH, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (eg, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE HCT Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE HCT Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with labetalol HCl is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Periodic determination of serum electrolytes to detect possible electrolyte imbalance from the thiazide should be performed at appropriate intervals.

Drug Interactions: ***Labetalol HCl:*** In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor, as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Hydrochlorothiazide: Insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazide drugs may increase the responsiveness to tubocurarine.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity.

In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when TRANDATE HCT and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions: ***Labetalol HCl:*** The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Hydrochlorothiazide: Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides may decrease serum protein-bound iodine (PBI) levels without signs of thyroid disturbance.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Labetalol HCl:*** Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis. Reproduction studies performed in rats and rabbits dosed orally with labetalol HCl at doses up to ten and eight times the human dose, respectively, revealed no evidence of impaired fertility or harm to the fetus.

Hydrochlorothiazide: Hydrochlorothiazide is presently under study for carcinogenesis in rats and mice in the National Toxicology Research and Testing Program.

Hydrochlorothiazide was not mutagenic in *in vitro* Ames mutagenicity assays of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 or in *in vivo* mutagenicity assays of mouse germinal cell chromosomes and Chinese hamster bone marrow cell chromosomes. It was, however, mutagenic in inducing nondisjunction (96% frequency) in diploid strains of *Aspergillus nidulans*. Hydrochlorothiazide had no adverse effects on fertility in rats at a dose equivalent to the maximum recommended human dose (MRHD) and in mice at a dose equivalent to 25 times the MRHD (4 mg/kg, assumed body weight of 50 kg).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** The combination of labetalol HCl and hydrochlorothiazide was not teratogenic in rats and rabbits at oral doses up to approximately 15 and 80 times the MRHD of labetalol (1,200 mg) and hydrochlorothiazide (50 mg), respectively. In rabbits, maternal toxicity was observed with consequent fetotoxicity at the lowest dose tested (3.5 and 20 times the MRHD of labetalol and hydrochlorothiazide, respectively). The combination of labetalol and hydrochlorothiazide appeared to be more toxic in rabbits than was either of the drugs given alone.

Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD.

Available information indicates that hydrochlorothiazide at doses as high as 330 times the MRHD was not teratogenic in pregnant rats.

There are no adequate and well-controlled studies in pregnant women. TRANDATE HCT Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Labetalol HCl: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in the adult.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. However, thiazides appear in greater amounts in breast milk. Because of the potential for serious adverse reactions in nursing infants from hydrochlorothiazide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Caution should be exercised when TRANDATE HCT Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In general, the adverse effects of the combination are the sum of the adverse effects of the two components.

Labetalol HCl: Most adverse effects are mild and transient and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, other agents with solely beta-blocking activity used in the control groups led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist led to discontinuation in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, and drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, and increased sweating. ***Cardiovascular:*** Edema and postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

Labetalol HCl/hydrochlorothiazide: The following adverse reactions were derived from multicenter, controlled clinical trials of three months' duration comparing labetalol HCl plus hydrochlorothiazide to labetalol HCl or hydrochlorothiazide alone. The rates, which ranged from less than 1% to 6%, are based on adverse reactions considered probably drug-related by the investigators. If all reports are considered, the rates are somewhat higher (eg, dizziness, 16%, headache, 11%, fatigue, 9%), but the overall conclusions are unchanged.

Body as a Whole: Asthenia, leg cramps, fatigue, headache, malaise, pain, rigors, gout, increased appetite, creatine phosphokinase, and hypokalemia. ***Gastrointestinal:*** Abdominal pain, constipation, dyspepsia, flatulence, gastritis, and nausea. ***Central and Peripheral Nervous Systems:*** Dizziness, decreased libido, parethesia (usually scalp tingling), insomnia, paronina, and somnolence. ***Cardiovascular:*** Postural hypotension. ***Autonomic Nervous System:*** Ejaculation failure and impotence (based on a male population of 108). ***Respiratory System:*** Bronchospasm and rhinitis. ***Skin and Appendages:*** Rash. ***Urinary System:*** Micturition frequency, nocturia, polyuria, and urinary retention. ***Vision:*** Abnormal vision.

In addition, a number of other less common adverse events in patients who were taking labetalol HCl have been reported in clinical trials or the literature.

Cardiovascular: Postural hypotension, including rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild and transient and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus and positive antinuclear factor (ANF). ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Cholestasis with or without jaundice. ***Musculoskeletal System:*** Muscle cramps and toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, facial erythema, Peyronie's disease, and reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents. ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. ***Cardiovascular:*** Intensification of AV block (see **CONTRAINDICATIONS**). ***Allergic:*** Fever combined with aching and sore throat, laryngospasm, and respiratory distress. ***Hematologic:*** Agranulocytosis and thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis and ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Hydrochlorothiazide: Adverse reactions reported include:

Gastrointestinal System: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, consbpation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis.

Central Nervous System: Dizziness, vertigo, paresthesia, headache, and xanthopsia.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia.

Cardiovascular: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates, or narcotics.

Hypersensitivity: Purpura, photosensitivity, rash, urticaria; necrotizing angiitis (vasculitis, cutaneous vasculitis), fever; respiratory distress, including pneumonitis and pulmonary edema, and anaphylactic reactions.

Other: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision, and severe fluid and electrolyte derangements (rarely).

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Clinical Laboratory Tests: ***Labetalol HCl:*** There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested and, more rarely, reversible increases in blood urea.

OVERDOSAGE: ***Information concerning possible overdosage and its treatment appears in the full prescribing information.***

HOW SUPPLIED: ***In scored tablets containing 100/25, 200/25, or 300/25 mg labetalol hydrochloride/hydrochlorothiazide per tablet in bottles of 100 tablets.***

TRANDATE HCT Tablets should be stored between 2° and 30°C (36° and 86°F).

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The portrait of anxiety

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Please see adjacent page for brief summary of prescribing information.

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is often complicated

With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

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XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) ©

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

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■ High Specificity	■ Clinical testing shows GONOSTAT to be as specific, about 99%, as the culture procedure established by clinical trials.
■ Vancomycin Sensitive Gonococci	■ GONOSTAT can detect vancomycin-sensitive strains of gonorrhea, eliminating false negative culture results from selective media incorporating vancomycin.
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■ Ease of Transport	■ GONOSTAT has been proven to be the "test of choice" where on-site or nearby culture facilities are not available, or delayed transport may be a factor. ■ GONOSTAT can be delivered by regular or special mail in complete confidence. ■ GONOSTAT permits specimens to be gathered over several days and shipped in quantities where no emergency or urgency of diagnosis is required. ■ Gonorrhea testing can be virtually anywhere, allowing specimen collection by healthcare professionals in inner-city or isolated areas.
■ Low-Cost Equal to the Gold Standard in Gonorrhea Tests	■ GONOSTAT is equal in performance, or better in cases of vancomycin sensitive strains, to all currently approved methods for gonorrhea testing. GONOSTAT offers outstanding advantages in ease of use, transport, and test results at cost lower than even most inhouse testing procedures.
■ Savings	■ GONOSTAT, because of its elimination of complicated handling and transport problems, and its high specificity and sensitivity, can provide significant cost containment in gonorrhea testing to public health providers.

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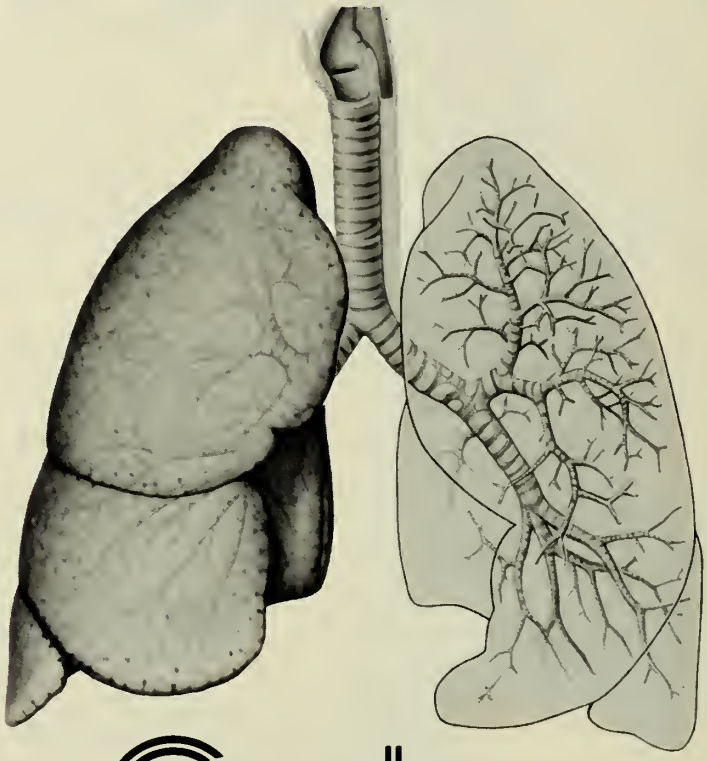

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Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus pyogenes* (group A β-hemolytic streptococci).

Contraindication:
Known allergy to cephalosporins.

Warnings:
CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever): 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
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- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly).

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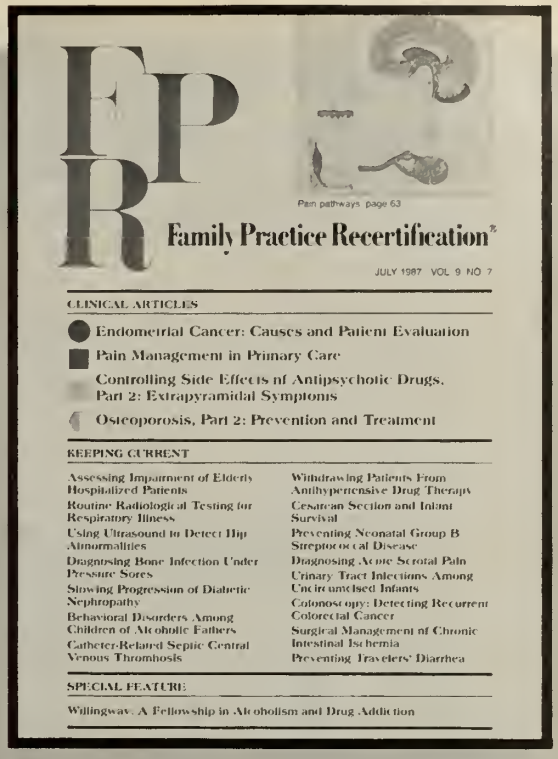
FPR
Pain pathways page 63
Family Practice Recertification
JULY 1987 VOL 9 NO 7
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Pain Management in Primary Care
Controlling Side Effects of Antipsychotic Drugs, Part 2: Extrapyramidal Symptoms
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ARIZONA

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

November 16-17—**Update on Management of Spina Bifida.** La Posada Resort, Scottsdale. Mon-Tues. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800)-BARROW-1.

January 22-24—**14th Annual Sports Medicine Symposium.** Holiday Inn Metrocenter, Phoenix. Fri-Sun. Contact: ArMA.

February 1-3—**State of the Art 2D/Doppler and Color Flow Imaging.** Sheraton El Conquistador Resort, Tucson. Mon-Wed. Contact: American College of Cardiology, (800) 253-4636, ext 226

February 4-6—**14th Annual Frontiers in Ophthalmology.** Scottsdale Hilton, Scottsdale. Thurs-Sat. Contact: Campbell Meeting Management for St Luke's Medical Center, (602) 838-6728.

February 25-28—**Arizona Academy of Family Physicians Scientific Assembly—1988.** Embassy Suites—The Biltmore, Phoenix. Thurs-Sun. Contact: AAFP, (602) 249-2021.

February 26-28—**Fourteenth Annual Scientific Session of the Arizona Society of Anesthesiologists.** Scottsdale Hilton Resort, Scottsdale. Fri-Sun. Contact: Beverly Richter, Arizona Society of Anesthesiologists, (602) 246-8901.

March 2-4—**11th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Secretary, Phoenix OB/GYN Society, (602) 241-1917.

March 6-9—**2nd Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sun-Wed. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1

March 10-12—**Practical Cardiology for the Family Physician.** La Posada Resort Hotel, Scottsdale. Thurs-Sat. Contact: American College of Cardiology, (800) 253-4636, ext 226.

March 10-12—**15th Annual Symposium: Selected Topics in Ischemic and Hemorrhagic Cerebrovascular Disease.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

March 22-25—**Pediatric Update 1988.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Paul C. Stillwell, MD, Phoenix Children's Hospital, (602) 239-5778.

PATHOLOGY

November 14-15—**Modern Applications of Immunohistochemistry in Human Tumor Diagnosis.** Arizona Society of Pathologists and U of A at Scottsdale Hilton, Scottsdale. Sat-Sun. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

February 10-13—**Immunology and the Clinical Practice of Allergy.** UCSD. Wed-Sat. 20 hrs. $245. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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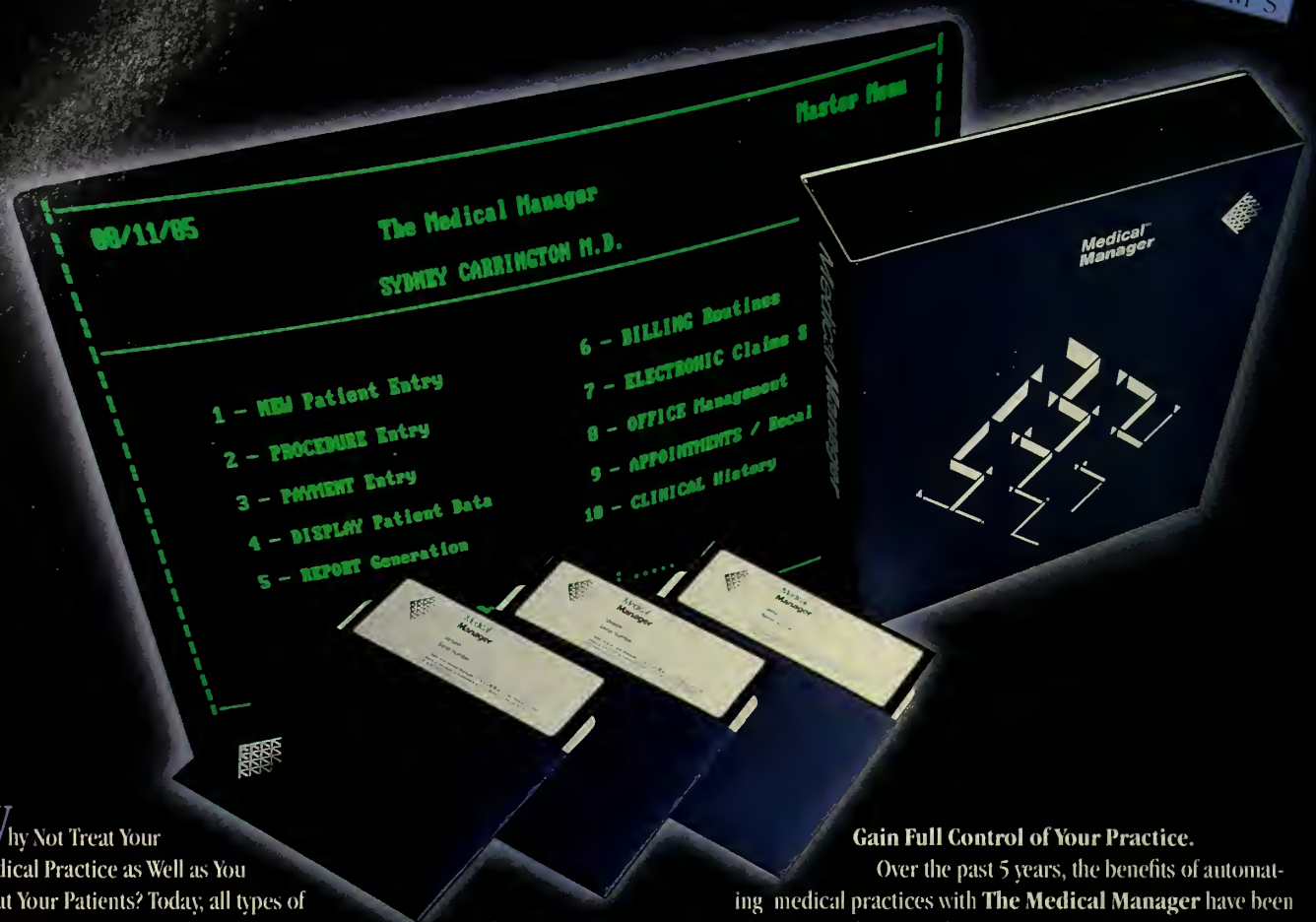

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(Continued from Page 634)

ANESTHESIOLOGY

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

January 31-February 5—**Biennial Western Conference on Anesthesiology: 1988 Clinical Update in Anesthesiology.** Toussaint Hospital Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. 22.5 hrs. $375. Contact: Murray G. Atnikov, c/o Box F110-63, Baline, WA 98230. (604) 874-5291.

March 19-20—**33rd Postgraduate Assembly.** Los Angeles Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: Laura Lee, Los Angeles Society of Anesthesiologists, PO Box 3465, Los Angeles, 90051-1465. (213) 483-1581 ext. 320.

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

CANCER

December 3-5—**Recent Advances in Occupational Cancer.** Northern California Occupational Health Center and UCSF at Miyako Hotel, San Francisco. Thurs.-Sat. $220. Contact: UCSF.

December 9—**23rd Northern California Cancer Conference.** N. T. Enloe Memorial Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th and The Esplanade, Chico 95926. (916) 891-7300.

December 12—**Bronchology Laser Cancer Symposium.** UCI at Long Beach. Sat. Contact: UCI.

February 4-6—**Third International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. 19 hrs. $310. Contact: UCSD.

February 25-27—**Second International Conference on Intracavitary Chemotherapy.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 18 hrs. $300. Contact: UCSD.

CARDIOLOGY

December 3-4—**Advanced Fetal Heart Rate Monitoring.** UCI at Newport Beach Marriott, Newport Beach. Thurs-Fri. Contact: UCI.

December 4-5—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

January 18-21—**Chest Imaging 1988.** San Diego Radiology and Research Education Foundation at the Hotel del Coronado, Coronado. Mon-Thurs. 22 hrs. $275. Contact: Dawne Ryals, Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 22-24—**Advanced Cardiac Life Support,** CPR Seminars at Ralph K. Davies Medical Center. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 28-30—**Clinical Nuclear Cardiology.** ACC at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. Contact: Mary Anne McIneny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 11-13—**Second Annual International Symposium: Clinical Strategies in Complex Valvular Heart Disease.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 16 hrs. $350. Contact: UCSD.

February 22-26—**Non-Invasive Diagnostic Techniques in Vascular Disease.** Scripps Clinic and Research Foundation at Sheraton Harbor Island Hotel, San Diego. Mon-Fri. 35 hrs. $550. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego, 92121. (619) 453-6222.

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

DERMATOLOGY

January 22-24—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess, San Diego. Fri-Sun. 20 hrs. $375. Contact J. SHiller, PO Box 84296, San Diego, 92138. (619) 223-2997.

EMERGENCY MEDICINE

March 23-25—**Advances in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. $300. Contact: UCSF.

May 11-15—**Tenth Annual Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith S. Bookstein/WMW, PO Box 1386, La Jolla 92038. (619) 454-3212.

INTERNAL MEDICINE

November 20-21—**Kuzell Institute Symposia.** Kuzell Institute for Arthritis and Infectious Diseases at Fairmont Hotel, San Francisco. Fri-Sat. 7 hrs. $25. Contact: Karen Allen, 200 Webster Street, R305, San Francisco 94115. (415) 561-1734.

December 20-24—**Immunology, Rheumatology and Allergy.** Symposium Maui at Royal Lahaina Resort, Maui. Sun-Thurs. 18 hrs. $395. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 1-4—**Specialties and Primary Practice.** Symposium Maui at Royal Lahaina Resort, Maui. Fri-Mon. 13.5 hrs. $295. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 19-23—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton, Beverly Hills. Tues-Sat. 40 hrs. Contact: UCLA.

February 7-12—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Incline Village. Sun-Fri. 18.5 hrs. $365. Contact: UCSF.

February 10-12—**21st Annual Recent Advances in Neurology.** UCSF. Wed-Fri. 15.5 hrs. $335. Contact: UCSF.

February 15-17—**Clinical Hematology and Oncology: 1988.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 4-5—**Gastrointestinal Endoscopy 1988.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Fri-Sat. Contact: David S. Cantor, MD, 50 Alessandro, Ste 410, Pasadena 91105. (818) 793-7114.

March 9-10—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Thurs. $250/$150. Contact: UCSF.

March 11-17—**Internal Medicine 1988: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Fri-Thurs. 54 hrs. $495. Contact: Jackie Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

November 16-20—**18th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

December 3-6—**Nebraska OB/GYN Society: 34th Scientific Session** at Bally's Hotel, Reno. Thurs-Sun. Contact: Marge Adey, Center for Continuing Education, University of Nebraska Medical Center, 42nd and Dewey Ave., Omaha, Nebraska 68105. (402) 559-4152.

December 4-5—**Environmental Exposure and Fetal Development (March of Dimes).** UCD at Sacramento Inn. Fri-Sat. Contact: UCD.

January 18-22—**19th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

February 7-11—**16th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki. Sun-Thurs. Contact: Ohio State University, 410 W 10th Ave, Columbus, Ohio 43210. (614) 293-8487.

(Continued on Page 638)

CONTINUING MEDICAL EDUCATION

(Continued from Page 637)

February 11-14—**43rd Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: Director of Medical Education, OB-GYN Assembly of California, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego, 92138. (619) 223-2997.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 92101. (619) 231-6760.

OPHTHALMOLOGY

December 10-11—**Ophthalmic Plastic and Reconstructive Surgery: Past, Present, and Future—A Tribute to Crowell Beard, MD.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Fri. 12 hrs. $325. Contact: UCSF.

March 18—**Visions in Ophthalmology '88.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Fri. 6 hrs. $75. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

PATHOLOGY

December 8—**Surgical Pathology: 1987.** UCSF. Tues. $30. Contact: UCSF.

PEDIATRICS

November 20-23—**9th Annual Las Vegas Seminars—Pediatric Update.** Los Angeles Pediatric Society at Caesar's Palace. Fri-Mon. Contact: Eve Black, Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305. (213) 757-1198.

January 16—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 4-6—**Current Concepts in Pediatric Medicine—1988.** Childrens Hospital and Health Center, San Diego at Holiday Inn, Embarcadero, San Diego. Thurs-Sat. Contact: Children's Hospital San Diego, 8001 Frost St, San Diego 92123. (619) 576-1700.

February 20-27—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Royal Lahaina Resort, Maui. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 22-24—**Pediatrics Update 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: J. Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 12—**Behavioral/Development Pediatrics Symposium: Stress, Vulnerability and Child Health.** UCSF. Sat. 6.5 hrs. Contact: UCSF.

PSYCHIATRY

November 30-December 1—**Behavioral Science as an Approach to Accident Prevention.** USC. Mon-Tues. 1.4 hrs. $375. Contact: USC.

January 21-24—**Health Science Response to Child Maltreatment—1988.** Children's Hospital and Health Center ar Hanalei Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Children's Hospital and Health Center, 8001 Frost St, San Diego 92123. (619) 576-1700.

January 24-29—**14th Annual Midwinter Program for Psychiatrists—Special Focus on Aquired Immune Deficiency Syndrome (AIDS).** UCD at Hyatt Lake Tahoe, Nevada. Sun-Fri. 25 hrs. Contact: UCD.

January 28—**Claudia Black: Loss of Childhood—And Recovery in Adulthood.** UCSD at Monterey Conference Center, Monterey. Thurs. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

February 6-7—**Intensive Short-Term Dynamic Psychotherapy With Highly Resistant Patients.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sat-Sun. $275. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

March 27-31—**Adapting to Social Change, Therapy, Technology and Services.** American Orthopsychiatric Association at Hilton Square, San Francisco. Sun-Thurs. Contact: ORTHO, 19 W 44th St, #1616, New York, NY 10036. (212) 354-5770.

RADIOLOGY

January 14-17—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Carlton Hotel, Laguana Niguel. Thurs-Sun. 20 hrs. $400. Contact: Dawne Ryals, Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 21-23—**Duplex Imaging.** UCSD at Inter-Continental Hotel, San Diego. Thurs-Sat. 18 hrs. $375. Contact: UCSD.

January 24-31—**Radiology for Emergency & Primary Care Physicians.** American Institute of Postgraduate Education and Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Kona, Hawaii. One Week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 3586, La Jolla 92038. (619) 454-3212.

January 29-31—**Fortieth Annual Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20hrs. $250. Contact: Los Angeles Radiological Society-MWOC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

February 2-6—**14th Annual Post Conference Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Tues-Sat. 18 hrs. $375. Contact: Los Angeles Radiological Society-MWRC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

SPORTS MEDICINE

January 17-22—**Sports Medicine: 1988.** UCD at Hyatt Lake Tahoe, Nevada. Sun-Fri. 28 hrs. $435. Contact: UCD.

SURGERY

November 21—**Primary Care Course.** American Society for Surgery of the Hand at Los Angeles. Sat. 7 hrs. Contact: Anne Turner, American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

December 6-12—**Temporal Bone Surgical Dissection—1987.** House Ear Institute at House Ear Institute, Los Angeles. Sun-Sat. 62 hours. $750-950. Contact: Antonio De la Cruz, MD, Director of Education, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 10-15—**Temporal Bone Surgical Dissection Courses—1988.** House Ear Institute. Sun-Fri. 62 hrs. Contact: House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 14-16—**Reperfusion—Restoration of the Compromised Circulation in the Coronary Vessels, Lungs, Carotid Circulation and the Hazarded Limb.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Thurs-Sat. 16 hrs. $300. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

January 15-16—**10th Annual Surgical Postgraduate Course: What's New in General Surgery—1988.** UCD at Sacramento Hilton Inn. Fri-Sat. 13 hrs. $175. Contact: UCD.

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November 18—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wed. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service, (117) VAMC, 16111 Plummer St, Sepulveda 91343. (818) 891-2473.

(Continued on Page 640)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 638)

November 22—**Controversy in Modern Medicine—1987.** Granada Hills Community Hospital and UCLA at Sheraton Universal Hotel, N Hollywood. Sun. 7 hrs. $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021.

December 3-5—**Fall Symposium on Back Pain.** American Back Society with St. Rose Hospital. Thurs-Sat. 16.5 hrs. Contact: American Back Society, 2647 E. 14th St., Oakland 94601. (415) 536-9929.

December 5—**Neuroimaging in the Management of Specific Clinical Problems of Brain and Spinal Cord.** UCLA. Sat. 10 hrs. $75. Contact: UCLA.

December 7-8—**Caring for the Patient With AIDS: Practical Aspects.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Tues. 13 hrs. $95. Contact: UCSF.

December 7-18—**Sexually Transmitted Disease (STD) Clinician Training Course—Comprehensive.** Long Beach Health Department and UCI. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Training Center, PO Box 6157, Long Beach 90806. (213) 427-7421.

February 2-4—**11th Annual: Neurology for Non-Neurologists.** UCSD and Neurology for Non-Neurologists Foundation at Holiday Inn Embarcadero, San Diego. Tues-Thurs. 21 hrs. $395. Contact: Edith S. Bookstein/NNN, PO Box 3586, La Jolla 92038. (619) 454-3212.

February 3-5—**Clinical Laboratory Molecular Analysis: Future Perspectives.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 24 hrs. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines, Rd, La Jolla 92037. (619) 457-8556.

February 11-13—**21st Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

February 12-13—**Comprehensive Care of the AIDS Patient: A Workshop.** UCSF. Fri-Sat. Contact: UCSF.

February 13-15—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs. Sat-Mon. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262. (619) 325-5588.

February 15-17—**Recent Advances in Geriatric Rehabilitation: What Is It? Who Needs It? What Works?** UCSD at Holiday Inn at the Embarcadero, San Diego. Mon-Wed. 18 hrs. $295. Contact: UCSD.

February 19-21—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs at Desert Hospital. Fri-Sun. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262.

March 11-12—**Diabetes Update.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. Contact: UCSF.

March 18-19—**Hematology: Neonatal, Pediatric and AIDS Related Issues.** Children's Hospital, Oakland at Berkeley Marina Marriott Hotel. Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Department, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

March 19-21—**Transfusion—Associated Infections and Immune Response.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. Contact: UCSF.

March 26-April 2—**Orthopedic Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Waiohai and Poipu Beach Hotels, Kauai. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 13-17—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Desert Princess Resort, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

IDAHO

February 13-20—**Controversies in Pulmonary Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

February 20-27—**Effective Treatment of Common Sports Injuries.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 4-6—**29th Annual Medical Winter Clinics—"You and Your Health."** Ada County Medical Society at Shore Lodge—Brundage Mountain for Alpine Powder and Nordic Skiing, McCall, Idaho. Fri-Sun. 11 hrs. $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 12-19—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

January 8-15—**Controversies in Wilderness Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Big Sky. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

February 18-20—**7th Annual Big Sky Pulmonary Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Thurs-Sat. Contact: ALA of Montana, 825 Helena Ave, Helena 59601. (406) 442-6556 or 1 (800) 252-6368 (in Montana).

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

December 3-5—**American College of Physicians, New Mexico Chapter—Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

December 11-12—**Trauma Update '87.** UNM Conference Center, Albuquerque. Fri-Sat. Contact: UNM School of Medicine, Office of CME, (505) 277-3942.

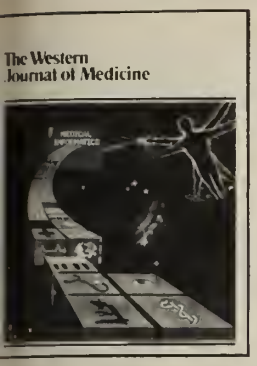
January 5-March 1—**History of Medicine Seminar—Modern Medicine.** David A. Bennahum, MD, Instructor. Medical Center Library, University of New Mexico, Albuquerque. 4-6 pm, Tuesdays.

February 25-27—**Santa Fe Ski Symposium—Hypertension—1988.** Santa Fe. Thurs-Sat. Contact: National Kidney Foundation of New Mexico, 1715 Girard, NE, Albuquerque 87106. (505) 266-4573.

February 26-28—**16th Annual Thoracic Society Lung Disease Symposium.** Santa Fe Hilton. Fri-Sun. Contact: Lung Association, (505) 265-0732.

(Continued on Page 644)

SPECIAL ISSUES



Medical Informatics

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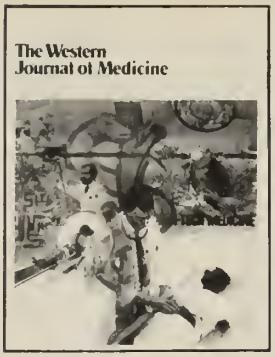

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—R. Paul Robertson, MD

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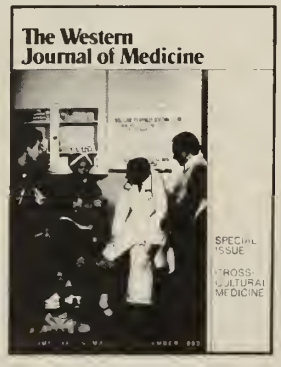

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GASTROENTEROLOGIST WANTED. Solo GI practitioner with busy, established, downtown, teaching hospital practice looking for associate to start July 1988 or sooner. Must be BC/BE, endoscopically adept, and enjoy pacific northwest life-style. Send CV to Number 55, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WASHINGTON, OREGON. Practice opportunities in urgent care and emergency department settings throughout the northwest. Malpractice provided in most locations. Competitive salaries. Recreational activities abound. Write or call L. Poschman, Northwest Emergency Physicians, 11808 Northup Way, Ste 110, Bellevue, WA 98005; (206) 828-6799.

CALIFORNIA, SAN FRANCISCO BAY AREA. Major HMO seeking BC/BE Emergency Physician to join staff of active Emergency Department in large, urban, academically-oriented medical center. Competitive salary, outstanding fringe benefits, and shareholdership are among the many advantages of joining Kaiser Permanente, the nation's leading HMO. Please address all inquiries to William Barnaby, MD, Emergency Department, Kaiser Permanente Medical Center, 280 W. MacArthur Blvd, Oakland, CA 94611.

GASTROENTEROLOGY position available with 35-member multispecialty group for a BC/BE physician; immediate opening with full range of benefits plus shareholder status on the central coast of California. Respond with CV to Recruitment, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

ONCOLOGIST, SAN FRANCISCO BAY AREA. Five-man group practice needs to replace retiring Oncologist. Practice includes Oncology and Internal Medicine. Position available July 1988. Send CV to Number 54, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FULL-TIME POSITION Available now for Family Practice physician in Vancouver, Washington. Call Helen Mosier, (206) 256-4500.

INTERNAL MEDICINE—SAN FRANCISCO BAY AREA. Immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical house staff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, and retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Circle, San Jose, CA 95119.

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PATHOLOGIST-AP-CP. To join three Pathologists, each of whom has subspecialty, in all new 18,000 square foot department. 300-bed hospital in northwest US. Work load requires fourth. Will be responsible for Micro and Infection Control, in addition to regular rotation. Preferably has advanced degree or fellowship in Microbiology. Competitive income, enviable climate with year 'round outdoor activities. Send CV with reply to Number 56, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ARIZONA. Emergency Medicine practice opportunities in the Phoenix metropolitan area. Active practice with double physician coverage; expanding group. Desirable location offering many outdoor recreational and cultural opportunities. Send CV to Ms Nancy Hayward, 1400 S. Dobson Rd, Mesa, AZ 85202 or call (602) 833-6180.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 640)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 8-13—**Utah Ophthalmological Society Annual Winter Meeting** (Sponsor: UOS). Mon-Sat. Little America Hotel, Salt Lake City. 15 hrs. Contact: Carol Leavitt, (801) 355-7477.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 19—**AHA Teleconference: Ethics: Conflicts of Value, Challenge of Care.** Spokane. Thurs. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

November 20-21—**Innovations in Newborn Care: A Challenge for the 90s.** Seattle. Fri-Sat. Contact: NW Hospital, (206) 364-2229.

November 27-December 10—**Emergency and Critical Care Down-under.** Sites in New Zealand and Australia. Fri-Thurs. Contact: Washington Chapter, American College of Emergency Physicians, Georgine Elich, Kailani World Travel, 1 (800) 542-5264 or (206) 671-1800.

December 4-5—**Medico-Legal Aspects of Neurology.** Seattle. Fri-Sat. Contact: U/W, Alice Kuramoto, (206) 543-1047.

December 4-5—**Northwest Urological Society Annual Meeting.** Portland, Oregon. Fri-Sat. Contact: Pamela Moore, (206) 441-9762.

December 5—**Washington State Urology Society.** Portland, Oregon. Sat. Contact: Patti Smith, (206) 441-9762.

December 5—**Plastic Surgery Education Foundation Teleconference: Rhinoplasty.** Spokane. Sat. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

December 5—**Medico-Legal Aspects of Neurology.** Seattle. Sat. Contact: U/W.

December 5-6—**Washington State Society of Anesthesiologists—Winter Meeting.** Seattle. Sat-Sun. Contact: Patti Smith, (206) 441-9762.

December 10—**AHA Teleconference: Obstetrical Liability II: Excellence Under Fire.** Spokane. Thurs. Contact: Sacred Heart Medical Center, Vicki Currer, (509) 458-5236.

December 11—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

January 20—**Health Effects of Wood Smoke.** Seattle. Wed. Contact: U/W, (206) 543-1069.

January 22—**Biliary Tract Diseases—Stones and Tumors.** Seattle. Fri. Contact: VMMC.

January 29-30—**Orbital Problems and Treatment: Plastic and Reconstructive Surgery (WSAO Annual Meeting).** Seattle. Fri-Sat. Contact: Patti Smith, (206) 441-9762.

February 4-5—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: U/W.

February 5—**Esophageal Disorders in Clinical Practice.** Seattle. Fri. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 647)

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(Continued from Page 642)

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WASHINGTON. Openings for career oriented Emergency Physicians, BC/BE in Emergency or primary medical specialty. In a Seattle metropolitan hospital with 35,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 South 43rd St, Renton, WA 98055.

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WORK PART-TIME. Position available for Internist or GP/FP with Internal Medicine experience in Primary Care Practice, northern California Sierra foothills community of 25,000. Share rotating practice with two other MDs; you work one week in three. Outpatient and inpatient responsibilities (no OB, no ICU) in modern, fully-equipped, 100-bed hospital. Minimum salary of $1,800/week (with incentives, actual will be around $2,200/week). Insurance, housing and meals provided N/C. Send CV to David Lomba, 133 'B' Ascot Ct, Moraga, CA 94556.

BC/BE INTERNIST with an interest in noninvasive Cardiology currently being sought for a large metropolitan area in the southwest. The opportunity is available for a full affiliation with this state-of-the-art group of physicians with a fully-established practice. Please forward current CV to Number 66, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORINA. FULL-TIME EM ATTENDING POSITION available at 233-bed teaching hospital in the heart of the San Joaquin-Sacramento River Delta. $75,000-$100,000 plus per year with flexible scheduling, camaraderie and paid malpractice. Send CV to Richard Buys, MD, PO Box 1020, Stockton, CA 95201 or call (209) 468-6818. Affirmative Action/Equal Opportunity Employer.

BC/BE INTERNIST/PRIMARY CARE PROVIDER. A three-physician group is seeking a fourth physician to join a well-established practice. Practice is located in Albuquerque, New Mexico. Wide range of recreational and cultural activities. For further information, please respond to Number 67, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEUROLOGIST. Visalia Medical Clinic, Inc, a 37-physician multispecialty group, is searching for a Neurologist to enter an active practice. Located in the San Joaquin Valley in California and serving a market area of approximately 350,000. Excellent hospital services and facilities. BC/BE. Compensation is incentive oriented with rapid advancement to full partnership. Excellent fringe benefits. Please respond to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

URGENT CARE CENTER. Phoenix, Arizona area. Career opportunity for the right physician with Family Practice background. Please send CV in confidence to Executive Director, Urgent Care, Mercy Services Corporation—Phoenix, 555 W. Catalina Dr, Ste 204, Phoeniz, AZ 85013.

ENDOCRINOLOGIST. Full-time BC/BE Endocrinologist for specialty practice in the metropolitan Phoenix area. Emphasis on all areas of Clinical Endocrinology, diabetes, and research. Laboratory and diabetes education program. Salary negotiable. Position available immediately. Send CV to Number 63, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEPHROLOGIST. Full-time BC/BE Nephrologist for specialty practice in the metropolitan Phoenix area. Large acute and chronic dialysis. CAPD, and transplantation patient load. Salary negotiable. Send CV to Number 64, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEVADA—EMERGENCY MEDICINE. An Emergency Department full-time staff position and medical directorship opportunities are currently available at client hospital in Fallon, Nevada, located one hour east of Reno. Full-service community hospital with low-volume Emergency Department. Competitive rate of reimbursement, occurrence malpractice insurance coverage, CME allowance. Director also receives health benefits which include dependents. For more details, contact George Tracy, Spectrum Emergency Care, 6275 Lehman Dr, Ste C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

BC/BE GENERAL INTERNIST with or without subspecialty, to associate with five-man Internal Medicine group in small northern California city. Modern, complete and expanding hospital. Generous salary plus percentage. Early partnership. Please reply to Number 62, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

APPLICATIONS ARE SOLICITED for the position of Chief of Staff at the Martinez VA Medical Center and Associate Dean for VA Affairs at the UC Davis School of Medicine. This position is jointly recruited with UC Davis, and will carry an academic appointment appropriate to the individual's qualifications. The candidate must be BC and have experience or demonstrate potential in the coordination and administration of academic and patient care programs with broad executive authority to direct utilization of resources to achieve institutional goals. The level of appointment will be commensurate with prior educational, clinical and administrative experience. Please send CV to Edward C. Gomez, MD, PhD, Associate Dean, Clinical Education, UCD, c/o VA Medical Center (11), 150 Muir Rd, Martinez, CA 94553. The VA is an Affirmative Action/Equal Opportunity Employer. Applications will not be accepted after December 30, 1987.

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEUROSURGERY. Visalia Medical Clinic has an opening for a BC/BE Neurological Surgeon to enter an immediate and active practice. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens. Two Neurosurgeons presently serving this area. Excellent hospital services and facilities. Must be BC/BE. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

SOUTH CENTRAL WYOMING. Immediate practice opportunity for BC/BE Urologist. Well-equipped JCAH hospital for a service area of approximately 20,000 population. No state or city income tax. Relocation incentives. Superior hunting, fishing, camping, snowmobiling. Three hours to Colorado ski area, five hours to Jackson Hole. One and one-half hours to the mountains. If interested, please send CV and references to D. Abels, DO, Chairman, Recruiting Committee or Richard Mills, Executive Director, Memorial Hospital of Carbon County, Rawlins, WY 82301; (307) 324-2221.

CALIFORNIA CENTRAL VALLEY. Desire BC/BE Family Practitioner to join busy two-man FP practice. Easy drive to San Francisco or mountains. Growing area; city of 40,000; good schools. Guarantee plus benefits. Reply to Number 59, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA. Emergency Medicine Faculty Positions. Immediate opportunities available for career-oriented Emergency Physicians who possess excellent clinical and teaching skills to join the faculty of Emergency Medicine department. BC in Family Practice, Internal Medicine, Surgery, and/or BE in Emergency Medicine. Our facility, located in southern California, averages 38,000 Emergency Department visits per year, is a level II trauma center, regional burn center and Neonatology Intensive Care center. These positions require a teaching commitment in a university-affiliated Family Practice training program. We offer a competitive remuneration package to include salary, malpractice insurance, time off and flexible scheduling. Send CV to Empire Medical Group, PO Box 3571, San Bernardino, CA 92413.

CENTRAL OREGON community seeks BE/BC Internist. 103-bed combination facility has ICU/CCU. Service area of 12,000. Coverage available by Internal Medicine group in neighboring town. Generous practice assistance package. An outdoorsman's winter and summer paradise! Contact Cynthia Lacro, Prosearch, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070.

VANCOUVER, WASHINGTON. BC/BE Family Practitioner, Gastroenterologist and General Internist to join a growing well-established, 40-physician multispecialty group. Clinic is in a high growth area with a multitude of outstanding recreational, cultural and educational opportunities in nearby Portland, Oregon, Mt. Hood and the Columbia Gorge. High-quality practice with excellent vacation and benefits package. Salary first two years, with potential for full partnership. Send CV to Roger R. Garretson, 700 N.E. 87th Ave, Vancouver, WA 98664.

UROLOGIST BC/BE. To be 2nd Urologist in a 36-physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package and excellent recreational, cultural and educational opportunities. Send CV to Search Committee, 55 W. Tietan, Walla Walla, WA 99362.

CARDIOLOGIST. 55-physician multispecialty medical group seeks full-time BC/BE Cardiologist. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

CONTINUING MEDICAL EDUCATION

(Continued from Page 644)

February 10-13—**Washington State Academy of Physician Assistants CME Conference.** Bellevue. Wed-Sat. Contact: Kory Diemert, (206) 441-9762.

February 19-20—**Medicine for Psychotherapists.** Seattle. Fri-Sat. Contact: VMMC.

February 20-27—**Maternal-Fetal Medicine Update.** Seattle. One week. Contact: U/W.

March 3-4—**Northwest Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Thurs-Fri. Contact: William Lassey, (509) 747-1012.

March 4-5—**Soft Tissue Surgery.** Seattle. Fri-Sat. Contact: VMMC.

March 11—**Recent Developments in Occupational Medicine.** Fri. Contact: U/W, (206) 543-1069.

March 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

March 25—**Update in Contrast Media: An Evening of Uroradiology.** Seattle. Fri. Contact: VMMC.

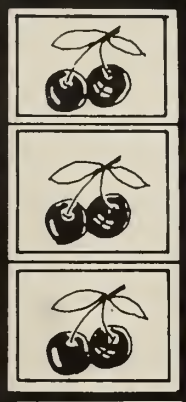
March 23-25—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

April 19—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Pattie Smith, (206) 441-9762.

WYOMING

February 28-March 6—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Jackson Hole. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

ADS GET RESULTS



CLASSIFIED INFO (415) 863-5522 EXT 244

PHYSICIAN WANTED

PULMONOLOGIST NEEDED, BC/BE. Excellent opportunity to establish private practice. No investment, guaranteed income. Growing service area population currently 90,000. 112-bed fully staffed hospital. Some IM necessary initially. In central California, Tulare offers family environment, abundant outdoor recreation, beautiful homes attractively priced, good schools, restaurants, shopping. Easy access to all California attractions. Contact Tulare District Hospital, Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

DIRECTOR, FAMILY PRACTICE RESIDENCY PROGRAM. St. Francis Medical Center affiliated with the University of Southern California School of Medicine and the Daughters of Charity National Health System (DCNHS) is a 416-bed comprehensive Medical Center operated by the Daughters of Charity of St. Vincent de Paul. St. Francis Medical Center is located in Lynwood, California which is in the southeast section of Los Angeles County. We are recruiting a BC Family Physician to serve as Director of our newly established Family Practice Residency Program. Our program is a 4-4-4 format and our first class began in July of 1987. This program has placed special emphasis on the training of family physicians in an urban environment. We require a candidate who is energetic, enthusiastic, and possesses strong administrative, teaching, researching, and leadership skills. Experience in new program development is desirable. Family Medicine Board certification is required, as is a minimum of two years' clinical practice in family medicine. Fluency in Spanish is highly desirable. Additional requirements include possession of, or eligibility for California licensure. We offer excellent salary and benefits. Please send a current CV and three references to Allan M. Hoffman, EdD, Director, Medical and Professional Education, St. Francis Medical Center, 3630 E. Imperial Highway, Lynwood, CA 90262; (213) 603-6174.

PHYSICIANS WANTED

PHYSICIAN/MEDICAL DIRECTOR. Full-time family practice physician needed for a community/migrant health center. Experience in medical administration as well as clinical experience helpful. BE or BC with Texas licensure preferred. Emphasis is on comprehensive ambulatory care, including OB care. Hospital inpatient care of registered patients required. The facility is located in a very pleasant rural community 85 miles southwest of San Antonio, Texas. Very competitive salary. Send CV or résumé with references to Rachel A. Gonzales, Executive Director, Uvalde County Clinic, Inc., 1009 Garnerfield Rd., Uvalde, TX 78801.

BEAUTIFUL COLORADO—Family Practice, Internal Medicine, and Occupational Physicians. Send CV to D. A. Franklin, MD, Medical Director, HealthWatch Medical Centers, 3400 Industrial Lane, Ste A, Broomfield, CO 80020.

ONCOLOGIST NEEDED, BC/BE. Excellent opportunity to establish private practice. No investment, guaranteed income. Growing service area population currently 90,000. 112-bed fully staffed hospital. Some IM necessary initially. In central California, Tulare offers family environment, abundant outdoor recreation, beautiful homes attractively priced, good schools, restaurants, shopping. Easy access to all California attractions. Contact Tulare District Hospital, Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

SAN FRANCISCO BAY AREA. BE/BC Internist needed immediately to join 20-physician Internal Medicine Department in large private multispecialty group. Preference given to candidates with IM residency at major academic institution. Competitive salary, liberal fringe benefits, and early corporate membership. Send CV or contact Robert H. Prall, MD, San Jose Medical Group, Inc., 45 S. 17th St, San Jose, CA 95112; (408) 282-7833.

ORTHOPEDIC SURGEONS. University of California, San Francisco-Fresno campus seeks two BC/BE Orthopedic Surgeons to join staff at Valley Medical Center of Fresno. The orthopedic service at VMC supports a busy trauma service and actively participates in teaching residents in General Surgery, Emergency Medicine and Family Practice. The position also offers private practice opportunities in a multispecialty group setting. Competitive salary and benefits. The central California location offers enjoyable and affordable California living. Address inquiries and CVs to Sergio Ilic, MD, Chief of Orthopedics, CCFMG, 2212 N. Winery, #130, Fresno, CA 93703; (209) 453-5058. Equal Opportunity Employer.

RADIOLOGISTS—Private practice opportunities available in Sparks, Nevada; Dallas, Texas; Lander, Wyoming. For details on openings, please call Eloise Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

CARDIOLOGISTS, FAMILY PRACTICE, INTERNISTS, OB/GYN, PEDIATRICIANS, PULMONARY MEDICINE—Private practice opportunities available in Washington, Nevada, California, Texas, and Louisiana. For details, please contact Eloise Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

BC/BE FAMILY PHYSICIAN. Full-time, for a four person family practice, in Fremont, northern California bay area. 250-bed hospital one-half mile away. Opportunity for partnership. Broad scope practice, no OB. Immediate opening. Please send inquiries to Tamara Cheney, MD, c/o The Center Medical Group, 2190 Peralta Blvd, Fremont, CA 94536.

NEUROSURGEON. EXPERIENCED BC PHYSICIAN to join established office adjacent to regional trauma center in northern California college town. Send CV to Number 69, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

EMERGENCY PHYSICIAN. Full- or part-time hospital position. BC/P in EM or equivalent combination of residency training and EM experience. California license required. Competitive remuneration, paid malpractice insurance, CE allowance, flexible scheduling, individual contract. 112-bed full-service hospital. In central California, Tulare offers family oriented environment, beautiful homes attractively priced, good schools, restaurants, shopping. Four hours drive to San Francisco, three and one-half hours to Los Angeles. Contact Andrew C. Jaramillo, MD, Tulare District Hospital, 869 Cherry St, Tulare, CA 93274; (209) 688-0821.

SAN FRANCISCO BAY AREA multispecialty group seeks Gastroenterologist, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

FAMILY PRACTICE PHYSICIAN. Southern California, Los Angeles suburb. BC/BE FP desired for group practice. Join five residency trained FPs in comprehensive practice. OB optional. Excellent hospital and support services. Salary, production, and benefits commensurate with experience. Malpractice paid. Send CV or call Mr Ed Myatt, Executive Director, Northridge Community Medical Group, 8330 Reseda Blvd., Northridge, CA 91324; (818) 886-1376.

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties.

Western States Physician Services
407 S. Clovis Ave, Ste 108, Fresno, CA 93727
(209) 252-3000

POSITION AVAILABLE IN SALT LAKE CITY FOR A PHYSICIAN. Will assist in licensing. Ideal for retired physician or one looking to slow down. Call Doug Klynstra 1 (517) 351-2620.

UROLOGIST. 55-physician, multispecialty medical group seeks full-time BC/BE Urologist. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

GASTROENTEROLOGIST BC/BE to be a second Gastroenterologist in a 36-physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package with excellent recreational, cultural, and educational opportunities. Send CV to Search Committee, Walla Walla Clinic, 55 West Tietan, Walla Walla, WA 99362.

NORTHERN CALIFORNIA-SIERRA FOOTHILLS. Four man Internal Medicine group seeking General Internist. Send résumé to PO Box 4142, Auburn, CA 95604.

NORTHERN CALIFORNIA-SIERRA FOOTHILLS. Four man Internal Medicine group seeking Non-invasive Cardiologist with interest in Internal Medicine. Send résumé to PO Box 4412, Auburn, CA 95604.

GENERAL INTERNISTS/CARDIOLOGIST/ENDOCRINOLOGIST. Opportunities in large prepaid group practice near San Francisco. Competitive salary. Liberal fringe benefits including paid educational leave, vacation, insurance, and retirement. Send CV to Mark Cole, MD, Department of Medicine, The Permanente Medical Group, 1200 El Camino Real, South San Francisco CA 94080.

CALIFORNIA—Kaiser Permanente office in central valley, rapidly growing new market area, seeking BC/BE physicians in the following specialties: Dermatology, ENT, Internal Medicine/Family Practice, General Surgery, Obstetrics/Gynecology, and Orthopedics. Address inquiries to Larry L. Coble, MD, Kaiser Permanente, 4785 N. First St, Fresno, CA 93726; (209) 221-4825.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

OXNARD (VENTURA COUNTY). New satellite facility of multispecialty group with 36 physicians has immediate position available for BC/BE General Internist. The growth oriented group is located on the California coast 60 miles north of Los Angeles. This family oriented community offers its residents a wide range of cultural experiences, and has an ideal suitable for year 'round outdoor recreation. Excellent benefits include guaranteed salary plus incentives, immediate health, life and dental insurance, income protection, and pension plan. No investment required. Estimated starting date of fall 1987. Send résumé to Recruitment MD, 2705 Loma Vista Rd, Ventura, CA 93003.

INTERNIST/FAMILY PRACTICE NEEDED, BC/BE. Join busy OB/GYN in new Women's Comprehensive Health Care Center. Ground-floor opportunity. Salary, malpractice paid. Growing service area population currently 90,000. 112-bed full-service hospital. In central California, Tulare offers family environment, abundant outdoor recreation, beautiful homes attractively priced, good schools, restaurants, shopping. Easy access to all California attractions. Contact Tulare District Hospital, Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

CARDIOLOGIST, NONINVASIVE, BC/BE to join six physician group—one Cardiologist, one Hematologist/Oncologist, two Gastroenterologists, and two Internists. Send CV to Hudson's Bay Medical Group, Inc., P.S., 2101 E. McLoughlin Blvd, Vancouver, WA 98661; (206) 695-1334.

DERMATOLOGIST NEEDED, BC/BE. Excellent opportunity to establish private practice with no investment, guaranteed income. Growing service area population currently 90,000. Proven financial potential. 112-bed full-service hospital. In central California, Tulare offers family environment, abundant outdoor recreation, beautiful homes attractively priced, good schools, restaurants, shopping. Easy access to all California attractions. Contact Tulare District Hospital, Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

INTERNIST—BC/BE, to join dedicated Internists in a practice committed to excellent care of older people. Send CV to J. Prazich, MD, 3919 Pringle St, San Diego, CA 92103.

TUCSON, ARIZONA. Family Practice, Internal Medicine, Urgent Care. CIGNA Healthplan has career opportunities in Tucson, Arizona. Professional liability coverage, paid vacations, CME, pension, and retirement benefits are provided. Please submit CV to Director or Physician Recruitment, CIGNA Healthplan of Arizona, Inc., 4907 E. Broadway, Ste 100, Tucson, AZ 85711; (602) 571-6517. Equal Opportunity Employer, M/F/H/V.

ENERGETIC PEDIATRICIAN, BE, wanted to join solo Pediatric practice. Good opportunity to build a large practice near major hospital with neonatal ICU, Burbank, California. (818) 843-6203, Dr Resnik for details.

SACRAMENTO AREA—RADIOLOGY—Interesting multioffice practice. Part-time and vacation coverage needed. Possible long-term association. Robert Swisher, MD, 729 Sunrise Ave—901, Roseville, CA 95661; (916) 786-9440.

GENERAL INTERNISTS. The University of California, San Francisco-Fresno campus seeks two General Internists for Chief of Medical Department Inpatient Services and Chief of Medical Department Outpatient Services positions, at Valley Medical Center, Fresno. Successful candidates should be BC/BE in Internal Medicine. Intensive care medicine experience for inpatient services candidates desirable. Valley Medical Center is a 417-bed acute care hospital with University affiliated residency and medical student training programs in all major specialties, including 21 residents in Internal Medicine and 18 full-time faculty. The central San Joaquin Valley offers delightful living conditions and ready access to coastal and mountain areas. Send CV to Roger Larson, MD, Chief of Medicine, CCFMG, 2212 N. Winery, #130, Fresno, CA 93703; (209) 453-5058. Equal Opportunity Employer.

CALIFORNIA, SAN FRANCISCO, SUBURBAN. Family Practice or Emergency Medicine physician to join group of five FP/EM MDs. $60,000 plus bonus to start. Four and one-half days per week and every fifth weekend. No OB; hospital care optional. Write G. N. Rogan, MD, 1482 Reliez Valley Rd, Lafayette, CA 94549, Immediate need.

GENERAL SURGEON—BE/BC. Outstanding opportunity for aggressive surgeon with a highly profitable, well-established, fee-for-service, multispecialty clinic. 14 physicians on staff. Ready made practice. Unmatchable guaranteed salary first year, then ownership. New hospital. Wonderful family town with nationally recognized school system and unequalled outdoor recreation possibilities. Telephone calls will not be accepted. Send CV to John Brust, Mesaba Clinic, 1814 14th Ave East, Hibbing, MN 55746.

OCCUPATIONAL/FAMILY PRACTICE. Excellent opportunities with the west coast's leading provider of Occupational/Family Practice medicine. Full-time/part-time positions throughout California and Washington (Seattle/Tacoma). Current license/CPR. Attractive salary/incentives/benefits/malpractice. Contact Personnel Director, ReadiCare, Inc., 446 Oakmead Parkway, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

OTOLARYNGOLOGIST (ENT). 55-physician multispecialty medical group seeks full-time BC/BE Otolaryngologist (ENT). Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

PARTNER DESIRED—BC/BE Radiologist to share hospital and office practice. Must enjoy general radiology, mammography, nuclear medicine, ultrasound and CT. Hands on experience in real time ultrasound helpful. Excellent salary and benefits. Early partnership. Will consider longer term locums. Send CV to Radiology, 5681 N. Fresno St, Fresno, CA 93710.

SAN FRANCISCO BAY AREA multispecialty group seeks Family Practitioner, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

ORTHOPEDIST. The west coast's leading Occupational/Family Practice medical provider has full-time/part-time opportunities for Orthopedic Specialist in California and Washington (Seattle/Tacoma). Attractive package includes: guaranteed salary, incentive bonus and benefits. Current license. Contact Personnel Director, ReadiCare, Inc., 446 Oakmead Parkway, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

OREGON—FAMILY PRACTITIONERS, INTERNISTS, PEDIATRICIANS. Private practice opportunities are immediately available in beautiful northwest Oregon. Call today to investigate this opportunity to practice challenging medicine in a hospital-supported surrounding, while enjoying an incomparable lifestyle in one of the Northwest's most scenic areas. Competitive first year guarantees offered to the selected candidate. Interview and relocation expenses absorbed by the client. For complete details, contact Jim Murphy, Spectrum Search, PO Box 27352, St. Louis, MO 63141; 1 (800) 237-6906; (314) 878-2280.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

FAMILY PRACTICE PHYSICIAN NEEDED, BC/BE, as associate for busy FP office. This excellent opportunity offers competitive salary, paid malpractice insurance. Growing service area population now 90,000. California license required. 112-bed full-service hospital. Located in central California, Tulare offers family oriented environment, abundant outdoor recreation, beautiful homes attractively priced, good schools, restaurants, shopping. Easy access to all California attractions. Please send CV or call Tulare District Hospital, Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

FAMILY PRACTICE PHYSICIANS—Discover the magic of the southwest. Experience New Mexico! Outstanding career opportunities for BC/BE FPs. Obstetrics preferred, malpractice paid. Contact your Physician Consultant at New Mexico Health Resources, PO Box 27650, Albuquerque, NM 87125; (505) 242-0633. No fee.

OB/GYN NEEDED, BC/BE. Join busy OB/GYN in new Women's Comprehensive Health Care Center. Ground-floor opportunity, salary, malpractice paid. Growing service area population currently 90,000. 112-bed full-service hospital. In central California, Tulare offers family environment, abundant outdoor recreation, beautiful homes attractively priced, good schools, restaurants, shopping. Easy access to all California attractions. Contact Tulare District Hospital, Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

EXCELLENT TEXAS OPPORTUNITIES in Cardiology, ENT, Family Practice, General Practice, General Surgery, Internal Medicine, OB/GYN, Oncology, Orthopedic Surgery, Pediatrics, and Vascular Surgery to practice in one of several lake area communities in the beautiful Piney Woods area of east Texas. Excellent quality of life, first year guarantee, etc. Other Texas opportunities available also. Reply with CV or call Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; (512) 331-4164.

FAMILY PHYSICIAN. BC/BE. Established practitioner in beautiful Huntington Beach, California seeking new associate in rapidly expanding practice. Moving to new, larger office on modern hospital campus. Competitive guarantee with incentive, full benefits, and opportunity for full partnership. Send CV to Ms Debbie Mundy, Thomure Medsearch, 569 Melville, St. Louis, MO 63130, or call 1 (800) 443-3634.

NEW MEXICO. BC/BE Primary Care Physician for 500-bed psychiatric/geriatric hospital. Exciting programs in an exciting location, with superb climate, recreational and cultural benefits. Base salary $70,017 plus optional on-call salary supplement to $10,000. Fringe benefits are 21%, including paid malpractice and license fees, 2.5% per year retirement. Contact Philip Taulbee, MD, Medical Director, Las Vegas Medical Center, Box 1388, Las Vegas, NM 87701; (505) 425-6711.

MEDICAL DIRECTOR—COLORADO BASED. Unique opportunity with a publicly held healthcare company that is embarking upon a national expansion. Will be responsible for comprehensive QA and risk management, physician recruitment and management of medical staff. Leadership qualities and management skills required. MD with MBA or Healthcare degree preferred. Compensation includes stock options and bonus incentives. Send CV to Sue Doty, Recruitment Coordinator, 3400 Industrial Lane, Ste 5-B, Broomfield, CO 80020.

INTERNIST/RHEUMATOLOGIST. 55-physician multispecialty medical group seeks full-time BE/BC Internist/Rheumatologist. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

SEVERAL OPENINGS AVAILABLE for Family Practitioners throughout western and central North Dakota. This large multispecialty group is seeking physicians for several satellites. All positions include a lucrative salary guarantee, full benefit package, and coverage. For more information, contact Durham Medical Search, Inc., 6300 Transit Rd, PO Box 478, Depew, NY 14043 or call 1 (800) 633-7724.

CALIFORNIA, OREGON AND WASHINGTON. BE/BC General Surgery practice opportunities available. Excellent compensation, practice package. income potential in communities offering high quality of life. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220-4199; (503) 256-2070.

PHYSICIANS WANTED, SAN JOSE. Forensic medical company looking for MD who is bright, creative, and able to assimilate multiple facts into medical reports. Primarily worker compensation referrals. Part-time initially. Send CV to Miss D. Salrin, 1875 Century Park East, Ste 1400, Los Angeles, CA 90067.

SAN FRANCISCO BAY AREA multispecialty group seeks Neurologist, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

CHAIRMAN, DEPARTMENT OF INTERNAL MEDICINE, KERN MEDICAL CENTER. A county operated teaching hospital is seeking a chairman for this UCLA affiliated department. The department has nine full-time and part-time members, 18 residency positions all currently filled with quality graduates. Qualifications: BC in Internal Medicine, established record of scholarly achievement in teaching and patient care, demonstrated management skills to direct a fully accredited residency program in an active public hospital and relate to other programs at Kern Medical Center and the UCLA system. Candidate must be eligible for appointment to senior faculty position at UCLA and be licensed in the State of California. (The County of Kern is an Equal Opportunity Employer.) Address inquiries with CV to Paul Toot, MD, Chairman, Internal Medicine Search Committee, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

NEW MEXICO—FAMILY PHYSICIAN. Innovative practice in New Mexico mountain community needs third BC/BE FP. Salary guarantee with reasonable work schedule. Video available showing our practice style, area, and people. Gila Family Care, 1121 West St, Silver City, NM 88061.

THE COMMUNITY OF ARTESIA, NEW MEXICO is seeking a BC/BE General Surgeon to establish a private practice. Fully-equipped office with established referral patterns available for purchase. Community-based financial assistance may be available to the right individual. Artesia is a community of 14,000 located in southeast New Mexico. A great place to raise a family—peaceful community with year 'round recreation and excellent weather. Fully-equipped, 38-bed new hospital. Please submit CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, ext. 8300.

WASHINGTON, PSYCHIATRIST. 30 minutes from Seattle. Combine private office practice with inpatient care at progressive 27-bed psych unit in a 250-bed hospital. Wide spectrum of inpatient treatment programs and opportunities for specialization in growing Puget Sound city. (Service area of 350,000.) Solo or expense sharing group options with established psychiatrists, income guarantee negotiable. Post residency experience preferred. Proven ability to work effectively with an interdisciplinary patient care team. The Friedrich Group, Inc., 9284 Ferncliff Northeast, Bainbridge Island, WA 98110; (206) 547-7850 or (206) 842-5248.

FAMILY PRACTITIONER. Tulare County is seeking a BE/BC Family Practitioner to practice in an out-patient clinic which includes inpatient duties, with 14 physicians. Ability to perform simple OB required. The County provides a benefit package which includes malpractice insurance coverage. Consider a semi-rural lifestyle with cultural amenities of metropolitan areas easily accessed and Kings Canyon and Sequoia National Park nearby. Salary $89,724-$94,296 annually. Send CV to Tulare County Personnel, 2900 W. Burrel, Visalia, CA 93291, (209) 733-6266; Equal Opportunity Employer.

FAMILY PRACTITIONER. Visalia Medical Clinic has an opening for a BC/BE Family Practitioner to join a four-physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40-physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

EUGENE, OREGON. Well-established, eight-physician Family Practice group is seeking BC/BE Family Physician with interest in OB. Anticipate partnership after one year. Exceptional cultural and recreational opportunities. Home of University of Oregon. Please send CV to Rob Daugherty, MD, or Kendall Hills, MD, River Road Medical Group, 2400 River Rd, Eugene OR 97404, or call (503) 688-7527.

INTERNIST NEEDED FULL-TIME. Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to Medical Director, French Health Plan, 4131 Geary Blvd, San Francisco, CA 94118.

DIAGNOSTIC RADIOLOGY GROUP with extensive military, academic and private practice experience desires full-service practice opportunity. Expertise in all areas including MRI, CT, Doppler US, Mammography and Interventional Procedures. Prefer western states. Reply to Number 61, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

LOCUM TENENS, INC. (A Division of Jackson and Coker), can staff your practice from 2 weeks to 52 weeks, malpractice insurance for all 50 states, contact John Smith, 400 Perimeter Center Terrace, Suite 760 WJM, Atlanta, GA 30346; Tel. 1 (800) 544-1987.

LOCUM TENENS SERVICE
WESTERN PHYSICIANS REGISTRY

. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 710 Van Ness, San Francisco, CA 94102; (415) 673-7676.**

FOR SALE. Well-established Internal Medicine practice; two offices–Los Angeles and Beverly Hills. Gross $3,000,000 plus. $100,000 down and an additional $25,000 per year for four years. Qualified buyers only. Please reply to Number 37, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PRACTICES FOR SALE IN 25 STATES. Specialties include FP, IM, ORS, OPH, Pd, U, N, GS. Take a moment and call today. Jackson and Coker, (404) 393-1210, Bob Kinberger, consultant.

M-1080-OB/GYN—ORANGE COUNTY, CALIFORNIA. Traditional caring doctor retiring after 23 years. Excellent practice and hospital network. Financing available for qualified doctor. M-1092-RADIOLOGY—Los Angeles basin. High volume, desired location. Excellent profits. M-1095-ALLERGY—southern California. Traditional doctor. Quiet community. High growth. 90% asthma and dermatology. Collects $175K. Doctor will introduce. M-1097-ENT—Sun belt. High profit practice in close knit medical community. 18 years established. Excellent equipment. M-1034-PEDIATRICS—Los Angeles basin. 25 years established. Traditional doctor will assist in transfer and financing. 100% referral, third generation patients. M-1052-INTERNAL MEDICINE. Prestigious practice in desired west Los Angeles area. Endocrinology background helpful. Excellent medical community. Practice enjoys security of faithful and affluent patient base. Annual collections over $400K. M-1058-CARDIOLOGY. Outstanding practice associated with prestigious hospital. Grossing $600K with low overhead. One of the United States' best living areas. M-1084-INTERNAL MEDICINE. Prestigious Palm Springs. Gross $600K, net $385K. Call Professional Practice Sales at (714) 832-0230.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 9-11, 1988, Loew's Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1988, date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1988, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1988, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1988, Laughlin.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1988, Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1988, date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1988, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1988, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

CLASSIFIED ADVERTISING 642, 646, 647, 648, 649, 650
CNA INSURANCE 546
COOPERATIVE OF AMERICAN PHYSICIANS 639
DEPARTMENT OF CORRECTIONS 630
DLC DIAGNOSTICS 635
DOCTOR/PATIENT INTERCOM 535
ELI LILLY & COMPANY
Keflet 632
FAMILY PRACTICE RECERTIFICATION 633
FHP PROFESSIONALS 627
GEIGY PHARMACEUTICALS
Lopressor 527, 528
GLAXO
Trandate 625, 626
Zantac 529, 530, 531, 532
HOFFMANN-LA ROCHE LABORATORIES
Dalmane . . . . . 2nd cover, 511, 512
Rocephin . . . . . 3rd and 4th covers
INSURANCE CORPORATION OF AMERICA 536
KNOLL PHARMACEUTICALS
Isoptin 543
MARION LABORATORIES
Carafate 544, 545
MEAD JOHNSON
BuSpar 523, 524, 525, 526
MERCK, SHARP AND DOHME
Vasotec 537, 538, 539, 540
MONY FINANCIAL SERVICES 643
JM PRINCETON COMPANY 630
PRINCETON PHARMACEUTICALS
Corgard 520, 521
A. H. ROBINS COMPANY
Micro-K 518
SMITHKLINE BECKMAN
Dyazide 548
SOUTHERN CALIFORNIA PHYSICIANS
INSURANCE EXCHANGE 513
SYNTEX LABORATORIES
Anaprox 541, 542
TECHNOLOGY MANAGEMENT AND
MARKETING, INC. 631
UNITED STATES AIR FORCE 645
UNITED STATES ARMY 526
UNIVERSITY MICROFILM 544
UPJOHN COMPANY
Micronase 547
Motrin 514, 515, 516
Xanax 628, 629, 630
THE WESTERN JOURNAL OF MEDICINE
Special Issues 641
Subscription 517

Rocephin® ROCHE® IV·IM

ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

SURGICAL PROPHYLAXIS Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e g , vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e g , during coronary artery bypass surgery)

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure

SUSCEPTIBILITY TESTING. Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients This appears to be reversible on discontinuation of therapy In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management

PRECAUTIONS: *GENERAL*· Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY. Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum

ROCEPHIN® (ceftriaxone sodium/Roche)

duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin Exercise caution before administration to hyperbilirubinemic neonates, especially prematures

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia palpitations and epistaxis

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g , dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION)

Also supplied as a sterile crystalline powder as follows

ADD-Vantage Vials** containing 1 gm or 2 gm equivalent of ceftriaxone

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 9 gm dextrose hydrous, USP added

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 2 gm dextrose hydrous, USP added

NOTE Rocephin in the frozen state should not be stored above -20°C

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†Manufactured for Roche Laboratories, Division of Hoffmann-La Roche Inc , by Travenol Laboratories, Inc , Deerfield, Illinois 60015

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* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

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Please see adjacent page for summary of product information.

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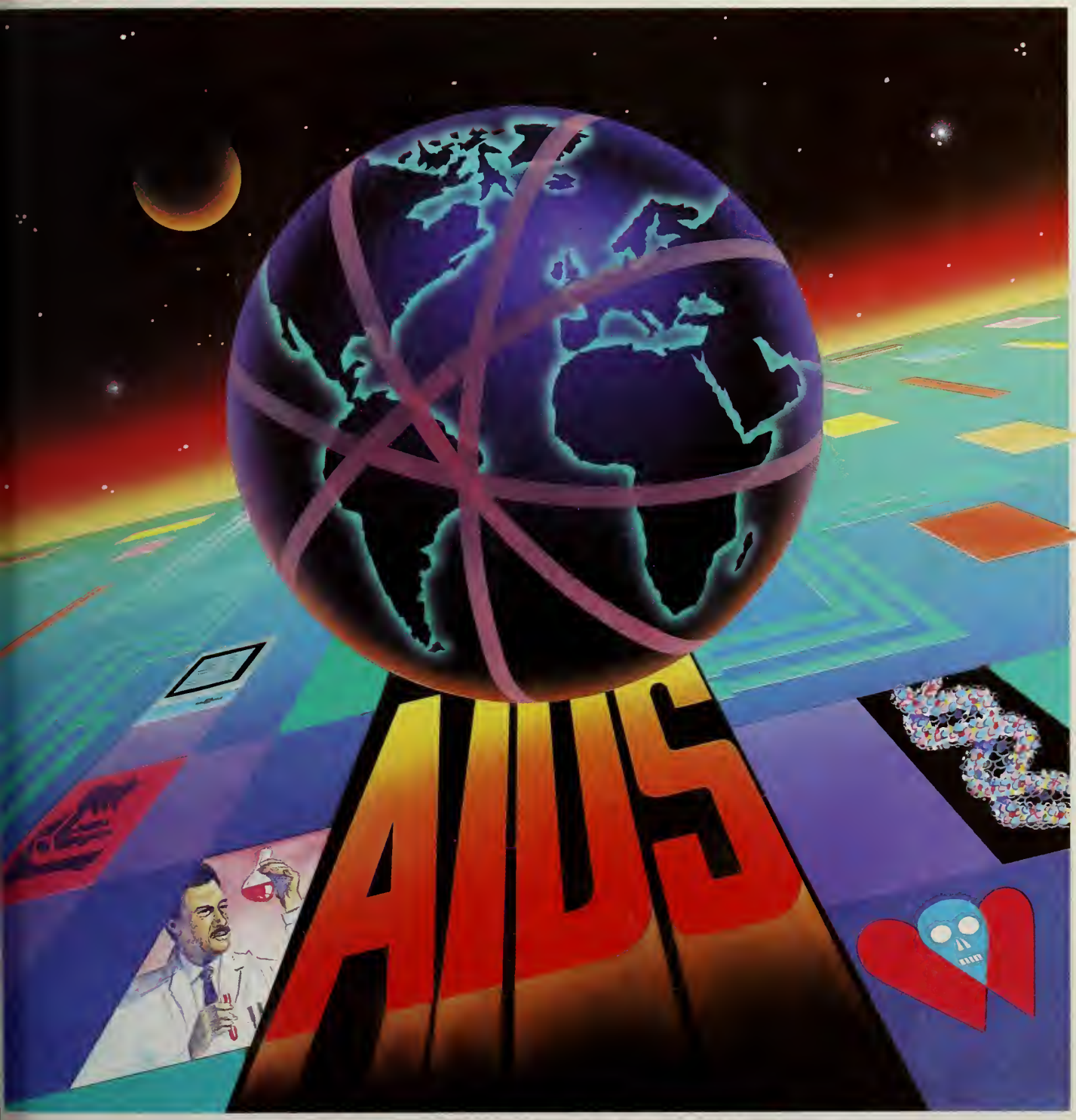

AIDS—A GLOBAL PERSPECTIVE

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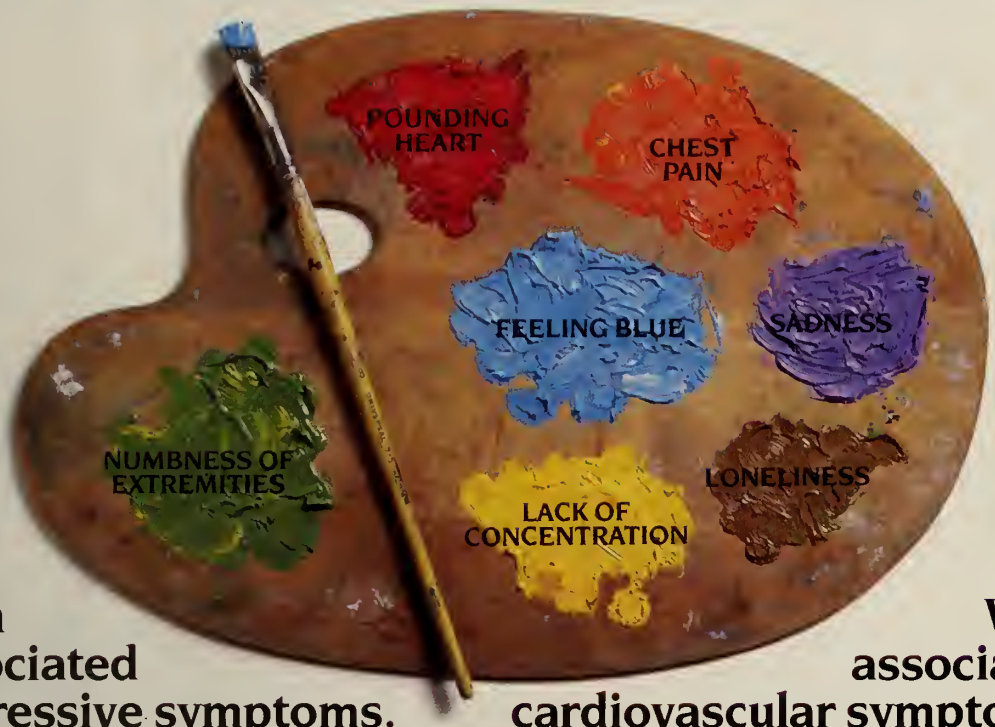
is often complicated



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Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

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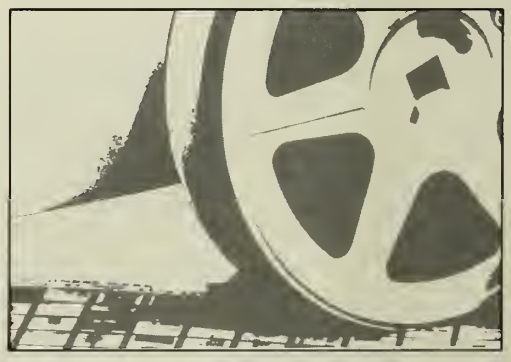

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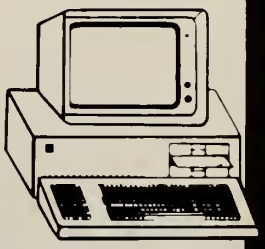

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CONTENTS

AIDS—A GLOBAL PERSPECTIVE

692 **The Deadly Grip of AIDS**

MALCOLM S. M. WATTS, MD

693 **AIDS—A Global Perspective**

JONATHAN M. MANN, MD, MPH

Dr Mann, the guest editor for this issue, is Director, Special Programme on AIDS, World Health Organization, Geneva.

694 **Global Epidemiology**

C. FORDHAM VON REYN, MD, and JONATHAN M. MANN, MD, MPH

From the Special Programme on AIDS, World Health Organization, Geneva.

702 **Human Immunodeficiency Virus and Related Retroviruses**

RAFAEL NÁJERA, MD; M. I. HERRERA, PhD, and R. de ANDRÉS, MSc

From the Centro Nacional de Microbiologia, Virologia e Inmunologia Sanitarias, Instituto de Salud Carlos III, Madrid.

709 **Clinical Manifestations and the Natural History of HIV Infection in Adults**

PETER PIOT, MD, and ROBERT COLEBUNDERS, MD

From the Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium; the Project Syndrôme d'Immunodéficience Acquise, Ministry of Public Health, and the Belgian-Zairian Medical Cooperation, Kinshasa, Zaire.

(Continued on Page 663)

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***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

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Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis—Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine < 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658H)

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(Continued from Page 659)

713 **Social, Cultural and Demographic Aspects of AIDS**

RENÉE C. SABATIER

From the AIDS Development Information Unit, Panos Institute, London.

716 **A New World With AIDS—Health Promotion as a Catalyst for Change**

ANTHONY J. MEYER, PhD

From the Health Promotion Unit, Special Programme on AIDS, World Health Organization, Geneva.

719 **AIDS Prevention and Control in Japan**

HIKO TAMASHIRO, PhD, DrPH; Y. KAWAGUCHI, MD, PhD, and M. ITO, MD, PhD

From the Special Programme on AIDS and the Programme for External Coordination, World Health Organization, Geneva, and the Ministry of Health and Welfare, Tokyo.

723 **Emerging Patterns of HIV Infection and Control in the Philippines**

MANUEL M. DAYRIT, MD, MSc; OFELIA T. MONZON, MD; VIRGINIA BASACA-SEVILLA, MD, and CURTIS G. HAYES, PhD

From the AIDS Prevention and Control Committee, the Microbiology Department and Research Institute for Tropical Medicine and the Bureau of Research and Laboratories, Department of Health, and the Virology Division, US Naval Medical Research Unit No. 2, Manila, Philippines.

726 **Towards a National AIDS-Control Program in Uganda**

SAMUEL IKWARAS OKWARE, MD, MPH, DPH, MBChB

From the Department of Disease Prevention and Control, AIDS Control Program, Ministry of Health, Entebbe, Uganda.

(Continued on Page 664)

(Continued from Page 663)

730 **The French National Program for the Prevention and Control of AIDS**

ALAIN POMPIDOU
From the Faculté de Médecine Cochin and the Ministry of Health, Paris.

732 **The World Health Organization's Global Strategy for the Prevention and Control of AIDS**

JONATHAN M. MANN, MD, MPH
From the Special Programme on AIDS, World Health Organization, Geneva.

735 **Appendix 1—Special Programme on AIDS and Expanded Programme on Immunization—Joint Statement**

738 **Appendix 2—AIDS Cases Reported to WHO**

743 **Appendix 3—AIDS Cases Reported—By Country**

OTHER FEATURES

676 **In Memoriam**

679 **Continuing Medical Education Activities in Arizona; California, Hawaii and Nevada; Idaho; Montana; New Mexico; Utah; Washington; Wyoming**

683 **Subscription Information**

746 **Consultants for 1987**
The editors acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given to the journal during the past year.

748 **Volume Index**

762 **Classified Advertising**

772 **Wyoming Medical Society—Winter Meeting**

778 **Western State Medical Associations' Meetings**

★ Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.

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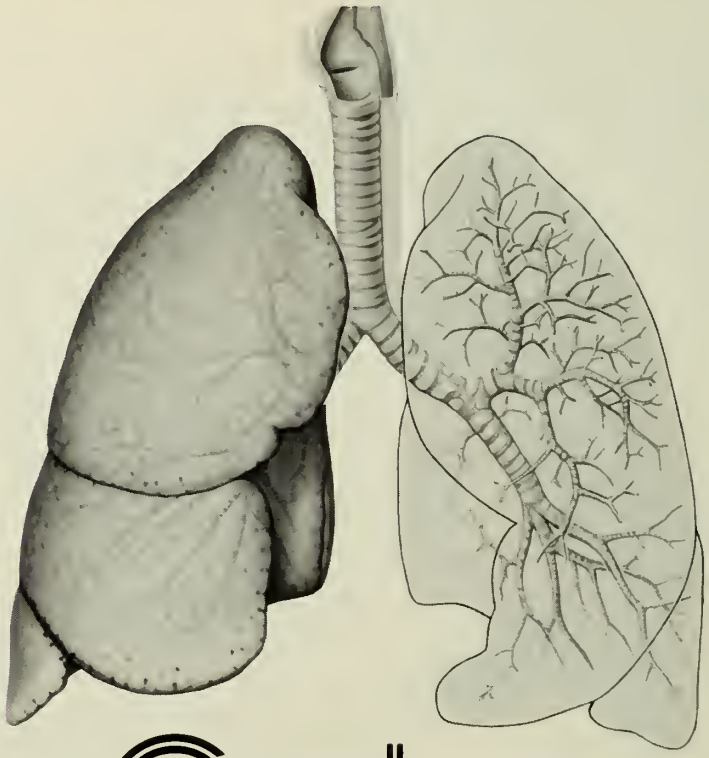

Ceclor®
cefaclor

250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae and *Streptococcus pneumoniae*
(ampicillin-susceptible and ampicillin-resistant)

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).

Contraindication:
Known allergy to cephalosporins.

Warnings:
CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)
Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever): 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology:
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children).
- Abnormal urinalysis; elevations in BUN or serum creatinine.
- Positive direct Coombs' test.
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly). [061787L]

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CARDIZEM®: A FULLER LIFE

diltiazem HCl/Marion

- **A remarkable safety profile**[1-6]
  The low incidence of side effects with Cardizem allows patients to feel better.
- **Protection against angina attacks**[1,5,7-9]
  The predictable efficacy of Cardizem in stable exertional and vasospastic angina allows patients to do more.*
- **A decrease in myocardial oxygen demand**
  Resulting from a lowered heart rate-blood pressure product.[5]
- **Compatible with other antianginals**[6†]
- **Safe in angina with coexisting hypertension, COPD, asthma, or PVD**[1,3,5,6]

90 mg GREATER DOSAGE FLEXIBILITY NEW 120 mg

*CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

CARDIZEM® diltiazem HCl/Marion

ANTIANGINAL PROTECTION PLUS SAFETY

Usual maintenance dosage range: 180-360 mg/day

Rx
Cardizem® (diltiazem HCl)
☐ 60 mg ☐ 90 mg
☐ 120 mg
Sig: tid

Brief Summary
Professional Use Information

CARDIZEM®
(diltiazem HCl) 30 mg, 60 mg, 90 mg, and 120 mg Tablets

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS
General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.*
Drug Interaction. *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*
Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.
Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*
Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration at doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*
There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*
Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.
In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.
The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 9/86

See complete Professional Use Information before prescribing

References: ***1.*** *Schroeder JS: Mod Med 1982;50(Sept):94-116.* ***2.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, W.B. Saunders Co, 1984, chap 39.* ***3.*** *O'Rourke RA: Am J Cardiol 1985;56:34H-40H.* ***4.*** *McColl D, Wolsh RA, Frohlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80.* ***5.*** *Frishman WH, Chorlop S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H.* ***6.*** *Shopiro W: Consultant 1984,24(Dec):150-159.* ***7.*** *O'Horo MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481.* ***8.*** *Strouss WE, McIntyre KM, Porisi AF, et al: Am J Cardiol 1982;49:560-566.* ***9.*** *Feldman RL, Pepine CJ, Whiffle J, et al: Am J Cardiol 1982;49:554-559.*

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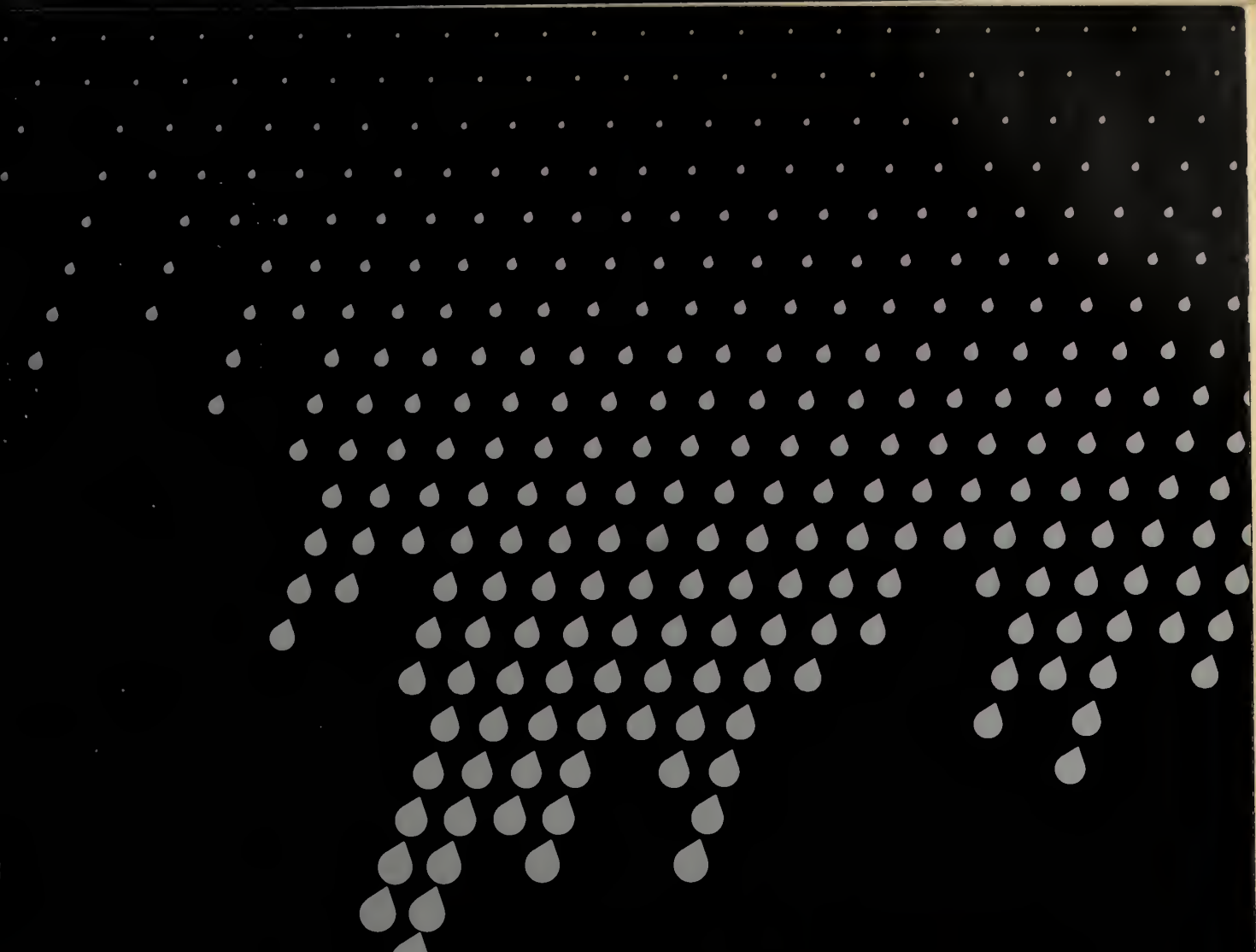


CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Only one tablet at bedtime

Controls nocturnal acid to relieve pain and heal duodenal ulcers

Heals active duodenal ulcers after 4 weeks in most patients*[1]

ZANTAC 300 mg h.s.	*270/320*	*84%*
ZANTAC 150 mg b.i.d.	*292/345*	*85%*

In well-controlled, double-blind, multicenter trials, ZANTAC 300 mg h.s. healed active duodenal ulcers in 84% of patients after 4 weeks. After 8 weeks, healing rates may be higher with ZANTAC 150 mg b.i.d. (92%) than with ZANTAC 300 mg h.s. (87%).

Relieves pain and other symptoms as effectively as ZANTAC 150 mg b.i.d.[1]

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Once-daily dosing may enhance compliance in patients for whom dosing convenience is important

Side-effects profile comparable to ZANTAC 150 mg b.i.d.[1-3]

Headache—sometimes severe—has been reported. Rare effects on the CNS, cardiovascular, GI, hepatic, and integumental systems have been observed, as well as rare cases of hypersensitivity reactions. See ADVERSE REACTIONS section of Brief Summary of Product Information before prescribing.

No significant interference with the hepatic cytochrome P-450 enzyme system at recommended doses

ZANTAC 300 mg h.s. had no significant drug interactions with theophylline or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications which decrease gastric acidity are administered.

s not known exactly how much acid inhibition needed to heal ulcers.

Glaxo / ROCHE

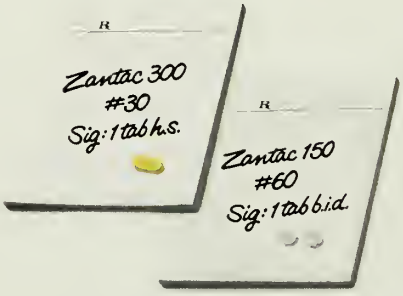
See next page for references and Brief Summary of Product Information.

IN ACTIVE DUODENAL ULCERS

Once-a-night h.s. therapy controls acid rain

Zantac 300
ranitidine HCl/Glaxo 300 mg tablets

Two effective regimens to treat active duodenal ulcers:



References: **1.** Data available on request, Glaxo Inc. **2.** Ireland A, Colin-Jones DG, Gear P, et al: Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984;2:274-275. **3.** Colin-Jones DG, Ireland A, Gear P, et al: Reducing overnight secretion of acid to heal duodenal ulcers. *Am J Med* 1984; 77 (suppl 5B):116-122.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects. Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, pr dominantly in severely ill elderly patients. Rare cases of reversib blurred vision suggestive of a change in accommodation ha been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and pr mature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, ar abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to least twice the pretreatment levels in 6 of 12 subjects receivi 100 mg qid IV for seven days, and in 4 of 24 subjects receivi 50 mg qid IV for five days. With oral administration there ha been occasional reports of reversible hepatitis, hepatocellular hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, gran locytopenia, thrombocytopenia) have occurred in a few patient Rare cases of agranulocytosis or of pancytopenia, sometimes wi marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown stimulation of any pituitary hormone by ZANTAC® (ranitidi hydrochloride) and no antiandrogenic activity, and cimetidin induced gynecomastia and impotence in hypersecretory patien have resolved when ZANTAC has been substituted. Howeve occasional cases of gynecomastia, impotence, and loss of libi have been reported in male patients receiving ZANTAC, but t incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mi erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospas fever, rash, eosinophilia) and small increases in serum creatinin

OVERDOSAGE: Information concerning possible overdosage and treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The curre recommended adult oral dosage is 150 mg twice daily. An alt nate dosage of 300 mg once daily at bedtime can be used f patients in whom dosing convenience is important. The adva tages of one treatment regimen compared to the other in a partic lar patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosa is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellis syndrome): The current recommended adult oral dosage is 150 m twice a day. In some patients it may be necessary to adminis ZANTAC® 150-mg doses more frequently. Doses should adjusted to individual patient needs, and should continue as lo as clinically indicated. Doses up to 6 g/day have been employed patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosa is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 m twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On t basis of experience with a group of subjects with severely impair renal function treated with ZANTAC, the recommended dosa in patients with a creatinine clearance less than 50 ml/min 150 mg every 24 hours. Should the patient's condition require, t frequency of dosing may be increased to every 12 hours or ev further with caution. Hemodialysis reduces the level of circulati ranitidine. Ideally, the dosage schedule should be adjusted so th the timing of a scheduled dose coincides with the end of hemodi ysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochlori equivalent to 300 mg of ranitidine) are yellow, capsule-shap tablets embossed with "ZANTAC 300" on one side and "Glaxo" the other. They are available in bottles of 30 (NDC 0173-0393-4 and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent 150 mg of ranitidine) are white tablets embossed with "ZANT 150" on one side and "Glaxo" on the other. They are available bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Prot from light. Replace cap securely after each opening.

August 19

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THE CALIFORNIA MEDICAL ASSOCIATION'S

1988 ANNUAL SESSION AND WESTERN SCIENTIFIC ASSEMBLY

March 4-9, 1988
Bally's Hotel and Reno/Sparks Convention Center

- ❑ **Western Scientific Assembly** offers more than 35 programs on issues such as wilderness medicine, AIDS, skin & breast cancer, alcohol & drug abuse, colorectal carcinoma and others
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For complete program and registration information call Susan Gunn-Schaefer at ☎ (415) 541-0900 or mail in the form below to:

California Medical Association
Attention: Susan Gunn-Schaefer
P.O. Box 7690
San Francisco, CA 94120-7690

Yes, please send me information on CMA's 1988 Annual Session.

Name _____

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In Memoriam

Arizona Medical Association

ATONNA, GUY B., Douglas. Died Sep 15, 1987, aged 80. Graduate of Boston University School of Medicine, 1933. Licensed in Arizona in 1943. Dr Atonna was a member of the Cochise County Medical Society.

CACKLER, C. STEPHEN, Tempe. Died Aug 2, 1987, aged 40. Graduate of University of Iowa, Iowa City, 1973. Licensed in Arizona in 1974. Dr Cackler was a member of the Maricopa County Medical Society.

CRUTHIRDS, ARCHIE E., Phoenix. Died Sep 7, 1987, aged 66. Graduate of Tulane University School of Medicine, New Orleans, 1921. Licensed in Arizona in 1923. Dr Cruthirds was a member of the Maricopa Medical Society.

California Medical Association

ARMSTRONG, ELWIN L., San Leandro. Died Sep 1, 1987, aged 76. Graduate of University of Southern California, 1936. Licensed in California in 1936. Dr Armstrong was a member of the Alameda-Contra Costa Medical Association.

AVON, HENRY A., Fremont. Died Aug 27, 1987, aged 64. Graduate of Northwestern University Medical School, Chicago, 1949. Licensed in California in 1950. Dr Avon was a member of the Alameda-Contra Costa Medical Association.

BECKER, SIDNEY F., Mission Viejo. Died Sep 8, 1987, aged 72. Graduate of University of Minnesota, Minneapolis, 1944. Licensed in California in 1969. Dr Becker was a member of the Orange County Medical Association.

BOROS, HAROLD H. Died Sep 8, 1987, aged 77. Graduate of University of Illinois, Chicago, 1937. Licensed in California in 1946. Dr Boros was a member of the Los Angeles County Medical Association.

BRADY, JAMES F., Alameda. Died Sep 9, 1987, aged 83. Graduate of University of California, San Francisco, 1933. Dr Brady was a member of the Alameda-Contra Costa Medical Association.

CELLA, ROBERT L., Martinez. Died Aug 28, 1987, aged 62. Graduate of New York Medical College, 1948. Licensed in California in 1957. Dr Cella was a member of the Alameda-Contra Costa Medical Association.

CHAMBERLAIN, CALVIN B. Died Sep 15, 1987, aged 80. Graduate of Tufts University School of Medicine, Boston, 1936. Licensed in California in 1947. Dr Chamberlain was a member of the Los Angeles County Medical Association.

DAVIS, STELLA, Santa Ana. Died Aug 1, 1987, aged 83. Graduate of Rush Medical College, Chicago, 1927. Licensed in California in 1935. Dr Davis was a member of the Orange County Medical Association.

FRY, LEONARD C., San Diego. Died Jul 18, 1987, aged 97. Graduate of St Louis University School of Medicine, 1925. Dr Fry was a member of the San Diego County Medical Society.

HANSEN, DANIELS D., Hemet. Died Aug 26, 1987, aged 56. Graduate of University of California, Los Angeles, 1956. Licensed in California in 1957. Dr Hansen was a member of the Riverside County Medical Association.

HENDRICKS, MAX, Wasco. Died Sep 10, 1987, aged 80. Graduate of University of Southern California, 1934. Licensed in California in 1934. Dr Hendricks was a member of the Kern County Medical Society.

JOHN, EDWARD A., San Jose. Died Jul 13, 1987, aged 75. Graduate of Loma Linda University, 1944. Dr John was a member of the Santa Clara County Medical Society.

KERN, MAXIMILIAN C., Richmond. Died Aug 26, 1987, aged 77. Graduate of Creighton University School of Medicine, Omaha, 1936. Licensed in California in 1943. Dr Kern was a member of the Alameda-Contra Costa Medical Association.

LONG, ALBERT E., San Francisco. Died Aug 31, 1987, aged 75. Graduate of University of Southern California, Los Angeles, 1943. Licensed in California in 1943. DrLong was a member of the San Francisco Medical Society.

LONG, JAMES C., Hemet. Died Aug 4, 1987, aged 77. Graduate of University of Southern California, 1936. Licensed in California in 1937. Dr Long was a member of the Riverside County Medical Association.

LYONS, HAROLD M. Died Sep 7, 1987, aged 71. Graduate of Stanford University School of Medicine, 1941. Licensed in California in 1941. Dr Lyons was a member of the Merced-Mariposa Medical Society.

MCGIRR, JOHN I. Died Sep 2, 1987, aged 70. Graduate of University of Nebraska, Omaha, 1943. Licensed in California in 1947. Dr McGirr was a member of the Los Angeles County Medical Association.

MCNAIR, JOEL N., Santa Ana. Died Jul 27, 1987, aged 68. Graduate of Columbia University, New York, 1944. Licensed in California in 1958. Dr McNair was a member of the Orange County Medical Association.

MACUMBER, HAROLD H., Ventura. Died Sep 4, 1987, aged 74. Licensed in California in 1945. Dr Macumber was a member of the Ventura County Medical Society.

MALONEY, HAROLD P., Oakland. Died Jul 31, 1987, aged 85. Graduate of St Louis University School of Medicine, 1926. Licensed in California in 1926. Dr Maloney was a member of the Alameda-Contra Costa Medical Association.

MINTZ, SAMUEL. Died Sep 8, 1987, aged 65. Graduate of University of California, Irvine, 1962. Dr Mintz was a member of the Los Angeles County Medical Association.

REID, ROBERT B., Perris. Died Jul 7, 1987, aged 88. Graduate of College of Medical Evangelists, 1931. Licensed in California in 1932. Dr Reid was a member of the Riverside County Medical Association.

RODNICK, NORMAN L. Died Jun 14, 1987, aged 63. Graduate of University of California, Irvine, 1962. Dr Rodnick was a member of the Los Angeles County Medical Association.

SHAW, EDWARD B., San Francisco. Died Sep 9, 1987, aged 92. Graduate of University of California, San Francisco, 1921. Licensed in California in 1921. Dr Shaw was a member of the San Francisco Medical Society.

SKILLEN, JANE. Died Jul 3, 1987, aged 91. Graduate of University of Michigan, 1928. Dr Skillen was a member of the Los Angeles County Medical Association.

SMITH, SAMUEL NEWLAN, San Marino. Died Aug 23, 1987, aged 71. Graduate of University of Southern California, Los Angeles, 1941. Licensed in California in 1941. Dr Smith was a member of the Los Angeles County Medical Association.

WICK, WARD, Santa Rosa. Died Aug 22, 1987, aged 72. Graduate of Northwestern University, Chicago, 1941. Licensed in California in 1949. Dr Wick was a member of the Sonoma County Medical Society.

WIMMER, SHIRLEY DOUGLAS. Died Aug 27, 1987, aged 88. Graduate of Stanford University, 1926. Licensed in California in 1926. Dr Wimmer was a member of the Los Angeles County Medical Association.

New Mexico Medical Society

PRIMER, BENJAMIN, Jr., San Marcos, Texas. Died Sep 6, 1987, aged 61. Graduate of University of Texas, Galveston, 1948. Dr Primer was an out-of-state member of the New Mexico Medical Society.

Utah Medical Association

ANDERSON, GRANT Y., Pleasant Grove. Died Jun 5, 1987, aged 63. Graduate of University of Pennsylvania School of Medicine, Philadelphia. Licensed in Utah in 1929. Dr Anderson was a member of the Utah County Medical Society.

GRAHAM, OSCAR J., Salt Lake City. Died May 22, 1987, aged 78. Graduate of Rush Medical College, Chicago. Licensed in Utah in 1940. Dr Graham was a member of the Salt Lake County Medical Society.

HASHIMOTO, EDWARD ICHIRO, Salt Lake City. Died Aug 23, 1987, aged 76. Graduate of Harvard Medical School, Boston, 1934. Licensed in Utah in 1935. Dr Hashimoto was a member of the Salt Lake County Medical Society.

POULSEN, J. ROBERT, West Valley City. Died Sep 2, 1987, aged 58. Graduate of University of Utah, Salt Lake City, 1958. Licensed in Utah in 1960. Dr Poulsen was a member of the Salt Lake County Medical Society.

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Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 22-24—**14th Annual Sports Medicine Symposium.** Holiday Inn Metrocenter, Phoenix. Fri-Sun. Contact: ArMA.

February 1-3—**State of the Art 2D/Doppler and Color Flow Imaging.** Sheraton El Conquistador Resort, Tucson. Mon-Wed. Contact: American College of Cardiology, (800) 253-4636, ext 226

February 4-6—**14th Annual Frontiers in Ophthalmology.** Scottsdale Hilton, Scottsdale. Thurs-Sat. Contact: Campbell Meeting Management for St Luke's Medical Center, (602) 838-6728.

February 10-13—**Sports Medicine—For All Practitioners.** La Posada Resort, Scottsdale. Wed-Sat. Sponsored by American College of Sports Medicine and Children's Medical Center, Oakland, California. Contact: Stuart C. Zeman, MD, Course Chairman, 2999 Regent Street, #203, Berkeley, CA 94705. (415) 540-8686.

February 25-27—**Contraception, Sterilization, and Sexually Transmitted Disease.** Paradise Valley Resort, Scottsdale. Thurs-Sat. Contact: Robin Murray, American College of Obstetricians and Gynecologists, (202) 863-2543.

February 25-28—**Arizona Academy of Family Physicians Scientific Assembly—1988.** Embassy Suites—The Biltmore, Phoenix. Thurs-Sun. Contact: AAFP, (602) 249-2021.

February 26-28—**Fourteenth Annual Scientific Session of the Arizona Society of Anesthesiologists.** Scottsdale Hilton Resort, Scottsdale. Fri-Sun. Contact: Beverly Richter, Arizona Society of Anesthesiologists, (602) 246-8901.

March 2-4—**11th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Secretary, Phoenix OB/GYN Society, (602) 241-1917.

March 6-9—**2nd Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sun-Wed. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1

March 10-12—**Practical Cardiology for the Family Physician.** La Posada Resort Hotel, Scottsdale. Thurs-Sat. Contact: American College of Cardiology, (800) 253-4636, ext 226.

March 10-12—**15th Annual Symposium: Selected Topics in Ischemic and Hemorrhagic Cerebrovascular Disease.** Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

March 22-25—**Pediatric Update 1988.** La Posada Resort Hotel, Scottsdale. Tues-Fri. Contact: Paul C. Stillwell, MD, Phoenix Children's Hospital, (602) 239-5778.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

February 10-13—**Immunology and the Clinical Practice of Allergy.** UCSD. Wed-Sat. 20 hrs. $245. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 680)

CONTINUING MEDICAL EDUCATION

(Continued from Page 679)

ANESTHESIOLOGY

December 20-25—**Immunology, Rheumatology, & Allergy.** Symposium Maui, Inc. at Royal Lahaina Resort, Maui. Sun-Thur. 18 hrs. $395. Contact: Symposium Maui, Inc. P.O. Box 10185, Lahaina, Hawaii 96761. (808) 897-8182.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles, CA 90054. (213) 669-2262.

January 31-February 5—**Biennial Western Conference on Anesthesiology: 1988 Clinical Update in Anesthesiology.** Toussaint Hospital Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. 22.5 hrs. $375. Contact: Murray G. Atnikov, c/o Box F110-63, Baline, WA 98230. (604) 874-5291.

March 19-20—**33rd Postgraduate Assembly.** Los Angeles Society of Anesthesiologists at Los Angeles Hilton Hotel. Sat-Sun. Contact: Laura Lee, Los Angeles Society of Anesthesiologists, PO Box 3465, Los Angeles, 90051-1465. (213) 483-1581 ext. 320.

May 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325-375. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

May 16-20—**5th International Symposium: Computing in Anesthesia and Intensive Care.** UCSD at US Grant Hotel, San Diego. Mon-Fri. 20 hrs. $300. Contact: UCSD.

June 16-19—**California Society of Anesthesiologists 1988 Annual Meeting** at Marriott Hotel, Anaheim. Thurs-Sun. 16 hrs. $150-225. Contact: California Society of Anesthesiologists, 1065 Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

CANCER

February 4-6—**Third International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. 19 hrs. $310. Contact: UCSD.

February 25-27—**Second International Conference on Intracavitary Chemotherapy.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 18 hrs. $300. Contact: UCSD.

CARDIOLOGY

January 18-21—**Chest Imaging 1988.** San Diego Radiology and Research Education Foundation at the Hotel del Coronado, Coronado. Mon-Thurs. 22 hrs. $275. Contact: Dawne Ryals, Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 20-30—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Tropicana Hotel, Las Vegas, Fri-Sat. 11-13 hrs. $225-$292. Contact: MER, 5808 S. Rapp St. Suite 202, Littleton, CO 80120. (800) 421-3756.

January 22-24—**Advanced Cardiac Life Support,** CPR Seminars at Ralph K. Davies Medical Center. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 28-30—**Clinical Nuclear Cardiology.** ACC at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 8-12—**3rd Annual Cardiovascular Conference at Hawaii.** ACC at Sheraton Royal Waikolua Hotel, Kona Coast, Hawaii. Contact: Mary Anne McInerny, American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814. (301) 897-5400.

February 11-13—**Second Annual International Symposium: Clinical Strategies in Complex Valvular Heart Disease.** UCSD at US Grant Hotel, San Diego. Thurs-Sat. 16 hrs. $350. Contact: UCSD.

February 22-26—**Non-Invasive Diagnostic Techniques in Vascular Disease.** Scripps Clinic and Research Foundation at Sheraton Harbor Island Hotel,San Diego. Mon-Fri. 35 hrs. $550. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego, 92121. (619) 453-6222.

March 11-12—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Tropicana Hotel, Las Vegas, Nevada. Fri-Sat.11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

March 21-23—**New Directions in Cardiac Rehabilitation.** ACC & Stanford University School of Medicine at Stanford. Mon-Wed. Contact: Registration Secretary EP Dept., ACC, Bethesda, MD (301) 897-5400.

March 25-27—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Inter-Continental Hotel, Maui, Hawaii. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

April 15-17—**Coronary Artery Disease: A Commemorative Symposium—75 Years Since Anitschkow and Herrick.** UCSF. Contact: UCSF.

April 18-27—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at the Inn at Rancho Santa Fe, Rancho Santa Fe. Mon-Wed. 40 hrs. $900. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Hilton Hotel, San Francisco. Wed-Thur. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 19-20—**Cardiology for the Non-Cardiologist.** UCI. Thurs-Fri. Contact: UCI.

June 6-8—**Advanced Echocardiography & Doppler Ultrasound 1988.** American College of Cardiology at Sheraton Harbor Island, San Diego. Mon-Wed. Contact: Registration Secretary, EP Dept. ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

June 30-July 2—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC, Orange Coast Heart Institute and Hoag Memorial Hospital at Westin South Coast Plaza, Costa Mesa. Thur-Sat. Contact: Registration Secretary, EP Dept., ACC, 9111 Old Georgetown Road, Bethesda, MD 20814.

DERMATOLOGY

January 22-24—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess, San Diego. Fri-Sun. 20 hrs. $375. Contact J. SHiller, PO Box 84296, San Diego, 92138. (619) 223-2997.

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

EMERGENCY MEDICINE

March 6-11—**9th Annual Mammoth Mt. Emergency Medicine Ski Conference.** UCI and Orange County Emergency Dept. Nurses Assoc. at Mammoth Lakes. Sun-Fri. 20 hrs. $350. Contact: CME Travel Services, 1615 S. Mission Road, Suite 3, Fallbrook 92028.

March 23-25—**Advances in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. $300. Contact: UCSF.

March 25-26—**Advances in Emergency Medicine: Toxicology and Infectious Diseases.** UCLA at San Diego Hilton, Mission Bay. Fri-Sat. 9 hrs. Contact: UCLA.

May 11-15—**Tenth Annual Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: Edith S. Bookstein/WMW, PO Box 1386, La Jolla 92038. (619) 454-3212.

INTERNAL MEDICINE

December 20-24—**Immunology, Rheumatology and Allergy.** Symposium Maui at Royal Lahaina Resort, Maui. Sun-Thurs. 18 hrs. $395. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 1-4—**Specialties and Primary Practice.** Symposium Maui at Royal Lahaina Resort, Maui. Fri-Mon. 13.5 hrs. $295. Contact: Symposium Maui, Inc., PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 19-23—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton, Beverly Hills. Tues-Sat. 40 hrs. Contact: UCLA.

February 1-12—**21st Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 15.5 hrs. $335. Contact: UCSF.

(Continued on Page 686)

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■ Vancomycin Sensitive Gonococci	■ GONOSTAT can detect vancomycin-sensitive strains of gonorrhea, eliminating false negative culture results from selective media incorporating vancomycin.
■ Ease of Use	■ Because GONOSTAT does not require a living gonococcal bacteria in the specimen, no special clinical handling – such as special media, CO_2 enriched environment, pre-incubation, or refrigeration is required for specimen transport. ■ Unless culture medium is quality-controlled, stored and inoculated properly, and promptly incubated in a CO_2-enriched atmosphere, culture may be unsatisfactory. No such precautions are required with GONOSTAT. ■ Costly physician or medical staff time to process specimens is eliminated by the use of GONOSTAT. ■ Familiar, easy to use Male and Female Collection and Transport Systems are provided with GONOSTAT. ■ GONOSTAT testing requires no mixing, batching, or formulating before or after specimen taking. ■ GONOSTAT culture collection kits need no special storage or handling before or after use.
■ Ease of Transport	■ GONOSTAT has been proven to be the "test of choice" where on-site or nearby culture facilities are not available, or delayed transport may be a factor. ■ GONOSTAT can be delivered by regular or special mail in complete confidence. ■ GONOSTAT permits specimens to be gathered over several days and shipped in quantities where no emergency or urgency of diagnosis is required. ■ Gonorrhea testing can be virtually anywhere, allowing specimen collection by healthcare professionals in inner-city or isolated areas.
■ Low-Cost Equal to the Gold Standard in Gonorrhea Tests	■ GONOSTAT is equal in performance, or better in cases of vancomycin sensitive strains, to all currently approved methods for gonorrhea testing. GONOSTAT offers outstanding advantages in ease of use, transport, and test results at cost lower than even most inhouse testing procedures.
■ Savings	■ GONOSTAT, because of its elimination of complicated handling and transport problems, and its high specificity and sensitivity, can provide significant cost containment in gonorrhea testing to public health providers.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 680)

February 7-12—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Incline Village. Sun-Fri. 18.5 hrs. $365. Contact: UCSF.

February 10-12—**21st Annual Recent Advances in Neurology.** UCSF. Wed-Fri. 15.5 hrs. $335. Contact: UCSF.

February 12-13—**Infectious Disease.** UCD at Sheraton Sunrise, Sacramento. Fri-Sat. Contact: UCD.

February 13-14—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $250 for both. Contact: UCI.

February 15-17—**Clinical Hematology and Oncology: 1988.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 21-26—**Emergencies in Internal Medicine: 11th Annual UCD Winter Conference.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 23 hrs. $395. Contact: UCD.

March 4-5—**Gastrointestinal Endoscopy 1988.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Fri-Sat. Contact: David S. Cantor, MD, 50 Alessandro, Ste 410, Pasadena 91105. (818) 793-7114.

March 9-10—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Thurs. $250/$150. Contact: UCSF.

March 11-17—**Internal Medicine 1988: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Fri-Thurs. 54 hrs. $495. Contact: Jackie Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

March 16-19—**Frontiers in Clinical Rheumatology.** UCD at Clarion Inn, Napa. Wed-Sat. Contact: UCD.

OB/GYN

January 18-22—**19th Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Mon-Fri. 35.5 hrs. $545. Contact: USC.

January 31-February 4—**OB/GYN Update 1988.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sun-Thur. Contact: UCD.

February 7-11—**16th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki. Sun-Thurs. Contact: Ohio State University, 410 W 10th Ave, Columbus, Ohio 43210. (614) 293-8487.

February 11-14—**43rd Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: Director of Medical Education, OB-GYN Assembly of California, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego, 92138. (619) 223-2997.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 92101. (619) 231-6760.

March 25-26—**GYN/Urology.** UCI at Hilton Riviera, Palm Springs. Fri-Sat. Contact: UCI.

April 21-23—**10th Annual Orange County OB/GYN Congress.** Orange County Obstetrical and Gynecological Society at Westin Hotel, South Coast Plaza, Costa Mesa. Thur-Sat. 15 hrs. $300. Contact: Paula Rogers, P.O. Box 1297, Orange 92668. (714) 978-1260.

June 30-July 3—**6th Annual Controversies in Obstetrics & Gynecology.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. Thur-Sun. Contact: The Center for Health Education, 2081 Atlantic Ave., P.O. Box 1428, Long Beach, 90801-1428. (213) 595-3811.

OPHTHALMOLOGY

January 31-February 4—**Tahoe Vitreoretinal Symposium.** UCD Retina Faculty at Granlibakken Ski Resort, Lake Tahoe. Sun-Thur. $360. Contact: Richard A. Murray, MD, 2701 "I" Street, Sacramento, CA 95816. (916) 442-4975.

March 18—**Visions in Ophthalmology '88.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Fri. 6 hrs. $75. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

PEDIATRICS

January 16—**Pediatric Cardiology for the Primary Physician.** Children's Hospital Oakland at Merritt Peralta Health Education Center, Oakland. Sat. 6 hrs. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

January 24-27—**13th Annual Winter Ski and Study Symposium.** California Chapters 1 & American Academy of Pediatrics at Caesars Tahoe Hotel, Lake Tahoe. Sun-Wed. $250. Contact: American Academy of Pediatrics, Chapter 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 29-31—**26th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott Hotel. Fri-Sun. 15 hrs. $225. Contact: Wayne Herbert, MD, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 4-6—**Current Concepts in Pediatric Medicine—1988.** Childrens Hospital and Health Center, San Diego at Holiday Inn, Embarcadero, San Diego. Thurs-Sat. Contact: Children's Hospital San Diego. 8001 Frost St, San Diego 92123. (619) 576-1700.

February 20-27—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Royal Lahaina Resort, Maui. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 22-24—**Pediatrics Update 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: J. Shiller, POBox 84296, San Diego 92138. (619) 223-2997.

March 12—**Behavioral/Development Pediatrics Symposium: Stress, Vulnerability and Child Health.** UCSF. Sat. 6.5 hrs. Contact: UCSF.

March 18-19—**Hematology: Neonatal, Pediatric & AIDS Related Issues.** Children's Hospital Oakland at Berkeley Marina Marriott Hotel, Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Dept. Children's Hospital, 747 52nd Street, Oakland 94609. (415) 428-3021.

April 8-9—**UCD Annual Pediatrics Program.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

April 29-30—**21st Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. 16.5 hrs. Contact: UCSF.

PSYCHIATRY

January 21-24—**Health Science Response to Child Maltreatment—1988.** Children's Hospital and Health Center ar Hanalei Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Children's Hospital and Health Center, 8001 Frost St, San Diego 92123. (619) 576-1700.

January 24-29—**14th Annual Midwinter Program for Psychiatrists—Special Focus on Aquired Immune Deficiency Syndrome (AIDS).** UCD at Hyatt Lake Tahoe, Nevada. Sun-Fri. 25 hrs. Contact: UCD.

January 28—**Claudia Black: Loss of Childhood—And Recovery in Adulthood.** UCSD at Monterey Conference Center, Monterey. Thurs. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

February 6-7—**Intensive Short-Term Dynamic Psychotherapy With Highly Resistant Patients.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sat-Sun. $275. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

March 27-31—**Adapting to Social Change, Therapy, Technology and Services.** American Orthopsychiatric Association at Hilton Square, San Francisco. Sun-Thurs. Contact: ORTHO, 19 W 44th St, #1616, New York, NY 10036. (212) 354-5770.

April 15-16—**3rd Annual Work and Mental Health Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. 12 hrs. $200. Contact: UCSF.

May 23-24—**Child Abuse.** UCD at Holiday Inn Holidome, Sacramento. Mon-Tue. Contact: UCD.

(Continued on Page 688)

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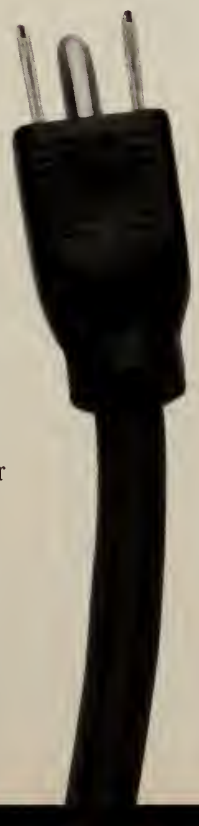

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(Continued from Page 686)

RADIOLOGY

January 14-17—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Carlton Hotel, Laguana Niguel. Thurs-Sun. 20 hrs. $400. Contact: Dawne Ryals, Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 21-23—**Duplex Imaging.** UCSD at Inter-Continental Hotel, San Diego. Thurs-Sat. 18 hrs. $375. Contact: UCSD.

January 24-31—**Radiology for Emergency & Primary Care Physicians.** American Institute of Postgraduate Education and Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Kona, Hawaii. One Week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 3586, La Jolla 92038. (619) 454-3212.

January 25-28—**Selected Topics in Nuclear Radiology—1988.** Dept. of Radiology, UCSD at Hotel Del Coronado, San Diego. Mon-Thur. 18.75 hrs. $375. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 29-31—**Fortieth Annual Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 20hrs. $250. Contact: Los Angeles Radiological Society-MWOC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

February 2-6—**14th Annual Post Conference Seminar.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Tues-Sat. 18 hrs. $375. Contact: Los Angeles Radiological Society-MWRC, PO Box 91215, Los Angeles 90009. (213) 642-0921.

February 21-24—**7th Annual UCSD Imaging & Intervention Conference.** UCSD, Dept. of Radiology at Hotel Inter-Continental, San Diego. Sun-Wed. 25 hrs. $400. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 7-11—**Neuroradiology Update.** UCSD at Hotel Del Coronado, San Diego, Mon-Fri. Up to 28 hrs. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 9-11—**8th Annual Current Approaches to Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: The Crest Organization, Outside CA (800) 222-8882; Inside CA (415) 595-2704.

April 10-15—**8th Annual San Diego Resident's Radiology Review Course.** UCSD at Town & Country Hotel, San Diego. Sun-Fri. Contact: Mary J. Ryals, P.O. Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

SPORTS MEDICINE

January 17-22—**Sports Medicine: 1988.** UCD at Hyatt Lake Tahoe, Nevada. Sun-Fri. 28 hrs. $435. Contact: UCD.

SURGERY

January 10-15—**Temporal Bone Surgical Dissection Courses—1988.** House Ear Institute. Sun-Fri. 62 hrs. Contact: House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 14-16—**Reperfusion—Restoration of the Compromised Circulation in the Coronary Vessels, Lungs, Carotid Circulation and the Hazarded Limb.** Scripps Memorial Hospital at La Jolla Marriott, San Diego. Thurs-Sat. 16 hrs. $300. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

January 15-16—**10th Annual Surgical Postgraduate Course: What's New in General Surgery—1988.** UCD at Sacramento Hilton Inn. Fri-Sat. 13 hrs. $175. Contact: UCD.

April 14-16—**Postgraduate Course in General Surgery.** UCSF. Thur-Sat. Contact: UCSF.

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January 1-4—**Specialties & Primary Practice.** Symposium Maui, Inc. at Royal Lahaina Resort, Maui. Fri-Mon. 13.5 hrs. $295. Contact: Symposium Maui, Inc. P.O. Box 10185, Maui, Hawaii. (808) 879-8182.

January 20—**Managing and Controlling Asbestos Contamination/Exposure.** USC Institute of Safety and Systems Management at Los Angeles. Wed. $160. Contact: USC.

(Continued on Page 757)

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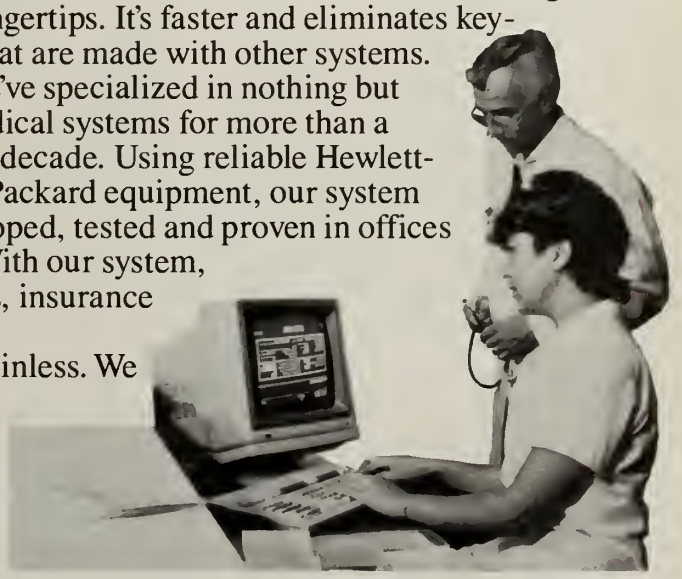

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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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David Greer

1943-1987

This special issue is dedicated to David Greer
Managing Editor from 1974 to 1987
with affection and respect
by the editors and staff of
THE WESTERN JOURNAL OF MEDICINE

The Deadly Grip of AIDS

For what is now almost a tradition, each year THE WESTERN JOURNAL OF MEDICINE has for its special December issue presented a topic that is at the cutting edge of problems or progress in health care. For this year the editors have chosen to address the looming problem of the acquired immunodeficiency syndrome (AIDS) from a global perspective. It so happened that Dr Jonathan Mann, Director of the Special Programme on AIDS of the World Health Organization in Geneva, has been a long-time member of the WJM Editorial Board, and when he was approached to be the Special Editor for this issue, he readily agreed. There is already much in the medical literature these days about AIDS and there is sure to be more, but the editors hope that this glimpse of a global view of AIDS at this time will be something a little different and perhaps a little special.

It is generally agreed that the human immunodeficiency virus (HIV) infection and its all too frequent consequence as the very fatal disease AIDS will become a genuine worldwide epidemic, if indeed it has not already. However or wherever it started, the disease is clearly spreading, and the modes of its transmission will be extremely difficult to control, human behavior being what it is. The absence of effective tools for either prevention or treatment and the reported progression of the disease set it apart from most of the infectious diseases with which present day physicians are readily familiar. One can hope that the virus will spontaneously attenuate or disappear as mysteriously as it has appeared, but so far there is little expectation that this will occur. More likely it will prove to be the cause of unprecedented worldwide fear, anxiety, disability and death for decades to come.

Living in the world as it is today, one can begin to wonder what effect this so far uncontrollable epidemic will have on health care systems and perhaps even health care values, and what will be its impact upon the various social, economic and political systems as they exist in this increasingly interdependent world.

It would seem certain that there will be profound effects on social mores and unprecedented stresses on economic resources and on the beliefs and priorities of politicians, legislators and governments at every level. Conceivably, and it might even be probably, all these pressures and stresses could eventually—and perhaps sooner than might be expected—become so severe as to bring about fundamental changes in how health care is conducted in this nation and in the world. It may be that as the social, economic and political pressures grow, the time will come when no nation will be able to afford the luxury of either the wasteful confrontation that now seems to be the order of the day in both health care and society or the similarly wasteful competition that exists in so many aspects of health care, competition that has been more or less mandated by our public policy. It could be that an unprecedented new era of genuine cooperation will become necessary among all those directly involved in health care. The sheer mass of the problems caused by the AIDS epidemic and by the reality of the interdependence of the independent segments of the social, economic and political systems may well force changes that cannot be imagined in December 1987.

At this moment in time the editors' purpose will have been served if this special issue of the journal begins to lift the curtain on the world drama of AIDS as it will certainly affect everyone everywhere, whether or not they, or anyone they know, contract the disease.

MSMW

AIDS—A Global Perspective

It is amazing, and humbling, to realize that in the late 1970s, the worldwide epidemic of human immunodeficiency virus (HIV) infection was silently underway and unnoticed. By the time its clinical manifestations were first recognized in the United States in 1981, the acquired immunodeficiency syndrome (AIDS) was already occurring on several continents. The worldwide scope of HIV infection and AIDS was not fully realized until 1986-1987; as of November 1, 1987, more than 62,000 AIDS cases were reported to the World Health Organization from 127 countries.

Yet, despite the delay in recognizing HIV and AIDS, the global mobilization to confront the HIV pandemic is well underway—and in record time. After several years, the World Health Organization (WHO) started to collect AIDS case reports and organize other exchanges of technical and policy information. The Special Programme on AIDS, officially created on February 1, 1987, has been entrusted with the responsibility to direct and coordinate the global strategy against AIDS—to lead the global fight. The Special Programme has designed the Global AIDS Plan, has mobilized sufficient resources to begin its implementation (which already involves more than 90 countries throughout the world) and has marshalled the support of every nation in the world.

In October 1987, the United Nations General Assembly, in discussing AIDS, approved a resolution calling for international cooperation in combatting this global threat to health. The General Assembly's actions are historic in two ways. First, AIDS can no longer be considered strictly a local, national or regional concern. Nor can it be thought to be a health problem for isolated or limited segments of society. In a resolute and clear fashion, the truly global scope and implications of AIDS have been stated.

The second historic feature of the General Assembly's debate was the explicit recognition that AIDS is not strictly a medical or health problem; rather, it has economic, social, cultural and political dimensions. Of course, this is not unique to AIDS, as the broad impact of disease on individuals, societies and history is well documented. Yet, as in so many other ways, AIDS has forced us to reexamine or reconsider vital and often unresolved issues.

In this special issue of THE WESTERN JOURNAL OF MEDICINE, we have sought to introduce American readers to some of the international dimensions of the HIV pandemic. Of particular interest will be descriptions of national AIDS programs in France, Uganda, the Philippines and Japan. Each of these countries has many experiences useful for the consideration of domestic AIDS issues.

To what extent can we learn from the experiences of others? To what extent can we learn from our own past experiences? These are central questions as we seek to develop strategies and policies for AIDS prevention and control.

Many have compared the global AIDS-control program to the successful smallpox-eradication program led by WHO. While global smallpox eradication exemplified the capacity for coordinated international health interventions, many differences between smallpox and AIDS are immediately apparent. Beyond the questions of vaccine, the clinical manifestations of infection and the basic epidemiology, we must recognize that smallpox had already been eradicated from the industrialized world when the WHO program started. In dramatic contrast, AIDS affects the industrialized world as severely as the developing world.

At WHO, we believe that research and efforts to prevent and control AIDS are firmly and irrevocably international and that we must learn from each other's national efforts how best to control AIDS.

Thus, in the world of the late 1980s, in which AIDS-related events in Uganda are reported promptly in the United States, and research findings in Australia become immediately relevant to policy discussion in Europe, we are witnessing a specific demonstration of the general principle that we are on a single "spaceship Earth." In the need for international cooperation, sharing and assistance prompted by the HIV pandemic, is there a message for us all?

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Global Epidemiology

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A total of 62,811 cases of the acquired immunodeficiency syndrome (AIDS) have been reported to the World Health Organization from throughout the world. Extensive epidemiologic studies have shown that human immunodeficiency virus (HIV) infections are transmitted by three routes: sexual, parenteral and perinatal. Three geographic patterns of transmission have been defined. In pattern I, transmission occurs predominantly among homosexual and bisexual men and urban intravenous drug abusers; transmission via blood products has been controlled; the male:female sex ratio is 10:1 or more; population HIV seroprevalence is low, and perinatal transmission is uncommon (for instance, United States, western Europe). In pattern II, transmission is predominantly heterosexual and perinatal; transmission via blood products exists but is being reduced; unsterile needles and other skin-piercing instruments cause some parenteral transmission (magnitude not known); the male:female sex ratio is 1:1, and population seroprevalence often exceeds 1% (central Africa, Haiti). In pattern III, AIDS cases are just being documented and are generally due to sexual exposure abroad or imported blood products (Middle East, Asia).

(Von Reyn CF, Mann JM: Global epidemiology, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:694-701)

The short and remarkable history of the epidemiology of the acquired immunodeficiency syndrome (AIDS) began in 1981 with the description of the clinical syndrome in California and New York.[1,2] In the six years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

Initially, clinical case definitions of AIDS were the principal tool of epidemiologic investigations, but after the discovery of etiologic retroviruses in 1983 and 1984[3,4] and the subsequent licensing of tests for antibody to human immunodeficiency virus (HIV) in 1985,[5] serologic data became available and increased the sophistication of epidemiologic studies. Because HIV infection in a population precedes the appearance of clinical AIDS by months to years, an optimal understanding of the current epidemiology must be based on an analysis of both HIV serologic data and reported AIDS cases.

This review considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines three geographic patterns of spread and then examines by continent the epidemiology of HIV infections.

Background

AIDS Case Definitions and Reporting

The initial clinical case definition of AIDS was published by the Centers for Disease Control (CDC) in 1982[6] and was subsequently adopted by the World Health Organization (WHO).[7] Strict criteria for the diagnosis of AIDS including documented Kaposi's sarcoma, *Pneumocystis carinii* pneumonia or other serious opportunistic infections were delineated. Subsequently the definition underwent minor revisions as other opportunistic infections and malignant tumors were recognized as indicative of AIDS. In 1985 serologic criteria were also added.[8]

In 1987 a broader CDC case definition for AIDS was proposed and adopted. The new definition adds AIDS encephalopathy, the HIV wasting syndrome and the presumptive diagnosis of indicator diseases to the previous definition[9] and is expected to increase the case count in the United States by 10% to 15%.[10]

Since clinical manifestations of AIDS differ in developing and industrialized countries, and since serologic confirmation is not available in many developing countries, WHO developed a clinical case definition at a workshop in Bangui, Central African Republic.[11] The WHO clinical case definition for adults is based on the "slim disease" presentation and includes both major and minor criteria (Table I).[7]

Studies in Zaire have shown the Bangui definition to have a specificity of 90% for adult HIV infection but a sensitivity of only 59%.[12] False-positives with this definition are often

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus
HTLV-IV = human T-lymphotrophic virus type IV
IV = intravenous
WHO = World Health Organization

due to the presence of tuberculosis because this disease often coexists with AIDS in Africa and has similar symptoms.

The true case count for pediatric AIDS is also underestimated by the surveillance definition,[8] since definitive diagnosis of opportunistic infection and exclusion of other causes of immunodeficiency are difficult in younger age groups. A broader classification system has been published, and a broader surveillance definition proposed.[13]

AIDS case reports to WHO are based on the standard CDC/WHO definition, the WHO Bangui definition and physician diagnosis. Not all countries report AIDS cases to the World Health Organization, and in some reporting countries with limited health care systems, case ascertainment is incomplete. Thus, both underreporting and the limitations of surveillance and clinical definitions contribute to the underestimation of AIDS cases worldwide.

Serologic Studies

Tests for antibody to HIV are the basis for most published HIV serosurveys. HIV antibodies are detectable by enzyme-linked immunosorbent assay one to two months after exposure and persist indefinitely.[14] In interpreting published reports of HIV seroprevalence, certain technical limitations of HIV antibody testing should be recognized. Some early reports of HIV seropositivity in Africa may have been inaccurate because of weak false-positive results due to the presence of malaria antibodies[15] and technical factors related to banked specimens.[16] The identification of additional human retroviruses (HIV-2, for example), some of which cross-react with HIV-1, further complicates interpretation of serologic data. In general, more recent studies and studies that discriminate between HIV-1 and HIV-2 will provide the most accurate data on seroprevalence.

Modes of Transmission

The human immunodeficiency virus has been isolated from blood[4] and serum[17] and from various body fluids, including semen,[18] cervicovaginal fluid,[19] breast milk,[20] tears[21] and saliva.[22] Detailed epidemiologic studies from throughout the world, however, have documented only three basic modes of transmission: sexual, parenteral and perinatal.

Sexual transmission occurs predominantly in homosexual and bisexual men and in heterosexual men and women.[23] Reports of transmission between homosexual women have been rare.[24] Risk factors for homosexual and bisexual transmission include numerous sexual partners, receptive anal intercourse and "fisting."[23,25]

Among heterosexuals transmission is related to the number of sexual partners, to contact with prostitutes[16,23] and, in some industrialized countries, to sexual contact with intravenous (IV) drug abusers.[26] The cumulative risk of HIV transmission to long-term heterosexual partners is about 50%, although the range of risk is wide.[27,28]

The risk of infection from a single heterosexual contact with an HIV-infected person is difficult to quantitate. It is dependent not only on the type of sexual activity but also on the infectivity of the partner. Calculated estimates have all been less than 1%.[29] However, in one study of artificial insemination with the introduction of semen from an infected donor directly into the cervix, four of eight women became infected.[30]

Parenteral transmission occurs with the transfusion of infected blood or blood products and with the use of unsterilized needles and syringes and other skin-penetrating instruments. In studies of single parenteral exposures, the risk of acquiring HIV infection appears related to the volume of inoculum. Recipients of a single unit of HIV-infected blood have an 89% or higher risk of acquiring infection.[31] Hemophiliacs who have received coagulation factor VIII concentrates have seroprevalence rates as high as 74% to 86%[25]; rates are lower among those who have received only cryoprecipitate.[32] Prospective studies of health care workers sustaining needle-stick injuries from AIDS patients have documented a risk of 0.5%.[33]

When needle-stick injuries have resulted in HIV transmission, the volume of blood injected has often been significant. The cumulative risk of HIV infection after multiple parenteral exposures to infected individuals is 51% to 87% among parenteral drug abusers in some high risk areas.[25] The risk of HIV infection from a single needle-sharing exposure is not known. Although the volume of blood inoculated is similar to that for a hospital-acquired needle-stick,[34] the drug abuser injects directly into the vein, a practice likely to create a single exposure risk higher than the 0.5% cited for needle-stick accidents among health care workers.

Perinatal transmission may occur before, during or shortly after birth. Although all three modes have been documented, the relative importance of each has not been defined. The overall risk of HIV transmission from an infected mother to infant ranges from 25% to 50%.[35-37] The human immunodeficiency virus has been isolated from a fetus aborted at 20 weeks[38] and from cord blood at birth.[39] Infection has been documented in infants delivered by cesarean section.[40] Postnatal transmission has been described in infants exposed to

TABLE 1.—*Clinical Case Definition for Adults with the Acquired Immunodeficiency Syndrome**

Requirements	*Major Signs*	*Minor Signs*
Disseminated Kaposi's sarcoma, or	Weight loss ≥10% of body weight	Persistent cough for >1 month
Cryptococcal meningitis or	Chronic diarrhea for >1 month	Generalized pruritic dermatitis
Two or more major signs plus one or more minor signs (in the absence of other causes of immunosuppression such as cancer or severe malnutrition)	Fever for >1 month (intermittent or constant)	Recurrent herpes zoster
		Oropharyngeal candidiasis
		Chronic progressive or/and disseminated herpes simplex
		Generalized lymphadenopathy

*From World Health Organization (Bangui).[7]

mothers who acquired HIV infection after delivery, with breast milk suggested as the possible means.[41]

Geographic Patterns of HIV Infection

Sexual, parenteral and perinatal modes of infection explain HIV transmission around the world, but there are significant geographic differences in both the relative frequencies of the three types of transmission and in the specific ways in which they occur in different cultures. Three major patterns are summarized in Table 2.

In pattern I, AIDS has been recognized since the late 1970s, and general population seroprevalence is low. Homosexual and bisexual intercourse predominate as the most common forms of transmission, with heterosexual transmission at a low level but expected to increase. Parenteral transmission is also significant and is related principally to IV drug abuse in large urban centers. Unsterile needles, other than those used by IV drug abusers, are not implicated in transmission. Transmission due to blood transfusion occurred between the late 1970s and 1985 but has now been controlled through the screening of blood supplies. Because rates of HIV infection among women are low, perinatal transmission is not common. It does occur among infants of female IV drug abusers, female sexual contacts of IV drug abusers and women from HIV-endemic areas. Pattern I has been recognized principally in industrialized nations, including the United States and many countries in western Europe.

In pattern II, HIV infection has been present since the mid-1970s, and transmission occurs among larger risk groups; hence, population seroprevalence is higher—often over 1%. Heterosexual transmission is the major mode of spread, and because of the resulting high seroprevalence rate among women, perinatal transmission is common. Blood transfusions have been a major risk, but HIV screening is now being introduced in many areas. Unsterile needles and syringes used for diagnostic or therapeutic purposes are potential factors in transmission, but the magnitude of this problem is difficult to assess.

In pattern III, HIV infection was introduced in the early to mid-1980s. Homosexual and heterosexual transmission are just now being documented, principally among prostitutes and persons from other known HIV-endemic areas or risk groups or those who have had contact with such groups. Most documented parenteral transmission has occurred among recipients of imported blood and blood products. Indigenous transmission by transfusion is a potential future problem, while transmission via IV drug abuse is not considered to be a major existing or future problem; perinatal transmission has not yet been documented.

Global Epidemiology

A total of 62,811 cases of AIDS have been reported to WHO by 127 countries as of November 1987. Figure 1 shows those countries that have reported one to nine cases and those that have reported ten or more. Table 3 shows that AIDS cases have been reported from every continent of the world. Figure 2 gives the worldwide epidemic curve by six-month reporting intervals. Because 70% of worldwide AIDS cases have been reported from the United States, a separate curve has been added to show cases from all other countries. Both curves are increasing at the same rate. WHO estimates that the actual number of AIDS cases in the world is 100,000 to 150,000 and that the number of HIV-infected persons is in the range of 5 to 10 million.

The Americas

As mentioned previously, AIDS was first described in the United States in 1981,[1,2] and reports suggest that the disease was present in the United States at least by 1978.[42] More than 44,000 cases had been reported by late 1987.[43] Transmission pattern I was first described in the United States, and cases continue to be distributed among risk groups in this pattern (Table 4).

Although reported cases of AIDS continue to double every 12 months, serologic data suggest that new acquisition rates for HIV have plateaued in at least one homosexual population under regular surveillance.[44] Screening of blood products (instituted in March 1985) and heat treatment of blood factor concentrates (beginning in October 1984) are expected to have virtually eliminated the new acquisition of HIV infection in the United States via blood products.[45,46] Because of the long incubation period for AIDS, however, any reduction in HIV transmission will not affect the number of reported AIDS cases for several years.

The largest increase in cases by risk groups from 1985 to 1986 was in the heterosexual contact category—a 131% increase.[26] Most heterosexual contact cases have been reported in women (83%), usually from contact with IV drug abusers and bisexual men (66%).[26] The estimated risk to health care workers had been studied most extensively in the United States and has been found to be extremely low.[47,48] Rare episodes of transmission of HIV have been reported from needle-

TABLE 2.—*Geographic Patterns of Infection With the Human Immunodeficiency Virus (HIV)*

	Pattern I		*Pattern II*		*Pattern III*	
Population seroprevalence	Less than 1%		More than 1%		Insignificant	
Male:female sex ratio	10:1 or greater		1:1		Undetermined	
Sexual transmission	Homosexual/bisexual	++	Heterosexual	++	Heterosexual	+
	Heterosexual	+			Homosexual	+
Parenteral transmission	Urban IV drug abuse	++	Blood, blood products	++	Imported blood	+
	Blood, blood products	+	Unsterile needles	+ ?		
Perinatal transmission	Female IV drug abuse	++	Female endemic	++	Not documented	
	Female sexual contacts of IV drug abusers	++				
	Females from HIV-endemic areas	+				
Examples	North America, Europe, some areas of South America, Australia, New Zealand		Central, eastern and southern Africa, Haiti		Middle East, Asia	

IV=intravenous, ++=predominant, +=present; + ? =present, magnitude unknown

sticks[49] and from mucous membrane and other nonparenteral exposure to infected blood.[50]

As of November 1987, AIDS has been reported in 628 children younger than 13 years in the United States.[43] The majority of these cases (77%) are infants of mothers at risk because of IV drug abuse or contact with IV drug abusers.[26] Other means of infection in the pediatric group include transfusion (12%), hemophilia/coagulation disorder (6%) and undetermined (5%).[43]

Brazil has reported the second largest number of cases in the Americas—1,965 by July of 1987. Transmission pattern I has been documented, with homosexual and bisexual men representing 75% of cases, hemophiliacs 5% and IV drug abusers and transfusion recipients 2% each.[51] Seropositivity rates for HIV among blood donors range from 0% in smaller cities to 0.14% in Sao Paulo[52] and 0.12% in Rio de Janeiro.[51] Despite the recognition of seropositive blood as a source of HIV transmission, implementing screening has been difficult with Brazil's largely commercial blood transfusion system.[51]

Although detailed epidemiologic data are not available for other countries in Central and South America, available reports suggest pattern I transmission (L. Mata, "AIDS in Costa Rica," May 1987, unpublished data). Antibodies to HIV have been reported in residents of rural Venezuela[53] and have been associated with acute malarial infection,[54] but since these results may represent nonspecific reactions, they must be confirmed by other investigators.[55]

In the Caribbean, Haiti has reported the largest number of AIDS cases—851 by July 1987. Review of autopsy and biopsy records suggests that the first AIDS cases appeared in Haiti in 1978, at about the same time as the first documented in the United States.[56] The clinical spectrum of cases in Haiti differs from that reported in the United States, with a higher

TABLE 3.—*Summary of Cases of the Acquired Immunodeficiency Syndrome (AIDS) Reported to the World Health Organization (WHO) as of July 15, 1987*

Continent	*Number of Cases*	*Number of Countries or Territories Reporting Cases*
Africa	5,857	37
Americas	48,591	41
Asia	208	18
Europe	7,477	27
Oceania	678	4
Total	62,811	127

TABLE 4.—*Cases of the Acquired Immunodeficiency Syndrome (AIDS) in Adults—USA and Europe*

Transmission Group	*USA,%**	*Europe,%†*
Homosexual/bisexual	66	64
IV drug abuser	16	15
Homosexual/IV drug abuser	8	2
Heterosexual	4	4
Hemophilia/coagulation disorder	1	4
Transfusion	2	3
Undetermined/other	3	8

IV=intravenous

*CDC, AIDS Weekly Surveillance Report, July 6, 1987.
†WHO Collaborating Centre on AIDS, Report No 13, March 31, 1987

COUNTRIES REPORTING ON AIDS TO WHO AS OF 11 AUGUST 1987
PAYS AYANT SIGNALE DES CAS DE SIDA A L'OMS AU 11 AOUT 1987

Figure 1.—The map shows countries reporting on the acquired immunodeficiency syndrome to the World Health Organization as of August 1987.

frequency of infections due to *Candida*, cryptosporidia and tuberculosis, and a lower frequency of *P carinii* pneumonia and infections due to atypical mycobacteria.[56] Epidemiologic studies have documented a pattern II transmission.[56-58] AIDS cases differ from controls in having a higher number of heterosexual contacts and more frequent histories of intramuscular injections; the reported male-to-female sex ratio is 3.3:1. Bisexuality is recognized as a risk factor among some men in Haiti,[56] and although it has been suggested that this often reflects male prostitution with tourists, there are no reliable medical data on male prostitution in Haiti.[59] Population seroprevalence is 6% to 8% among adults in urban areas,[60,61] and maternal infant transmission has been documented (N.A. Halsey, unpublished data, August 1987).

AIDS has also been reported from the neighboring Dominican Republic. In this country, with a higher per capita income and different cultural traditions than Haiti, initial reports suggest a type I pattern of transmission. Homosexual men predominate among reported AIDS cases, and seroprevalence studies show the highest rates among Dominican male homosexual prostitutes.[58] Male homosexual prostitution with tourists has been reported.[59]

Europe

In Europe 5,687 cases of AIDS had been reported by April 1987 to WHO by 27 participating countries (Table 5).[62] The pattern of transmission is type I, with minor deviations attributable to cases among non-Europeans. Among adults, the country of origin has been European for 91% of cases, an increase from 85% of total European cases reported in 1986.[62] Other geographic origins for adults include African (5%), Caribbean (2%) and others (2%). In Belgium 53% of adult cases have occurred in nonresidents, mostly from Africa. The percentage of African patients reported from Europe has been decreasing (13% in March 1985, 7% in March 1986, 5% in March 1987). The greatest number of cases has been reported from France, the Federal Republic of Germany, the United Kingdom, Italy and Spain. The highest rates per million people have been reported from Switzerland (34.9), France (29.7) and Denmark (29.4), compared with a figure of 140.2 for the United States for the comparable period.[62]

Countries reporting ten or fewer cases include Czechoslovakia, the German Democratic Republic, Iceland, Hungary, Luxembourg, Malta, Poland, Romania, the USSR and Yugoslavia. Between March 1986 and March 1987 the number of cases increased 123% among the 25 countries reporting for both intervals. The overall male:female sex ratio is 9:1, and the peak incidence is in the 30 to 39 year age range.

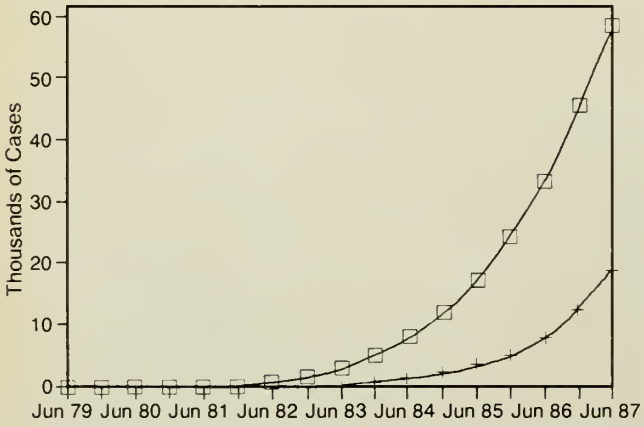

Figure 2.—Six-monthly cumulation of cases of the acquired immunodeficiency syndrome (reported to the World Health Organization as of September 9, 1987). □ = world total; + = world total, excluding the United States

Among adult Europeans the overall distribution of transmission groups is very similar to that of the United States (see Table 4), but there are significant differences by country. Homosexual and bisexual men form the largest group: 64% overall. However, in Denmark (87%), Sweden (85%) and the United Kingdom (89%), more than 80% of cases are in this risk group. The next largest category is heterosexual IV drug abusers, who represent a rapidly growing risk group in Europe[62] and account for 59% of cases in Italy and 52% in Spain. This group is younger (peak age, 20 to 29) and has a higher percentage of women than other risk groups with AIDS (male-to-female sex ratio 3:1).

The rates of HIV seropositivity among urban IV drug abusers vary within countries. In Italy, for example, rates are higher in Rome, Naples and Verona than in Milan and Cagliari.[63] In Scotland seroprevalence rates for this group are more than 50% in Edinburgh compared with 4.5% in Glasgow.[64,65]

Half of the reported heterosexual cases in Europe have occurred in patients from Africa and the Caribbean (106 of 236). High rates of seropositivity have been reported in European prostitutes. Studies in Germany have shown lower rates of seropositivity among registered prostitutes (1%) than among unregistered prostitutes (20% to 50%), many of whom are drug abusers.[66]

TABLE 5.—*Total Number of Cases of the Acquired Immunodeficiency Syndrome Reported in 27 European Countries and Estimated Prevalence Rates per Million Population, March 31, 1987*

Country	*Cases*	*Rate/M**
Austria	72	9.6
Belgium	230	23.2
Czechoslovakia	7†	0.5
Denmark	150	29.4
Finland	19	3.9
France	1.632	29.7
German Democratic Republic	3	0.2
Germany, Federal Republic	999	16.4
Greece	41	4.1
Hungary	3	0.3
Iceland	4	20.0
Ireland	19	5.3
Israel	38	9.0
Italy	664	11.6
Luxembourg	7	17.5
Malta	5	12.5
Netherlands	260	17.9
Norway	45	10.7
Poland	2	0.1
Portugal	54	5.2
Romania	2	0.1
Spain	375	9.3
Sweden	105	12.7
Switzerland	227	34.9
United Kingdom	729	12.9
USSR	3	0.0
Yugoslavia	10	0.4
Total	5,687	

*From AIDS Surveillance in Europe.[62]
†Slovak R.S 2, Czech S.R. 5.

The percentage of pediatric cases (age 15 or younger) is higher in Europe (3%) than in the United States (1%). This is due exclusively to an increased number of infected children between ages 2 and 5.

Africa

HIV infection was first suspected to be present in Africa when black Africans living in Belgium and France were diagnosed with AIDS in 1983.[67-69] Later that year AIDS was confirmed in patients from Zaire[70] and Rwanda[71] who had never traveled outside their countries. Serologic studies have shown the virus present in Africa in 1959.[72] Patients described in the early African reports differed in several respects from patients described in the United States. The African patients' most prominent symptoms were diarrhea, weight loss and a generalized pruritic maculopapular rash known as "prurigo." This presentation is similar to malnutrition, and is known locally as "slim disease."[73] Among African AIDS patients tuberculosis and cryptococcosis are more common and *P carinii* pneumonia less common than among AIDS patients in the United States. Atypical Kaposi's sarcoma occurs in AIDS patients in both Africa and the United States.[74]

The epidemiologic features of the African cases were also different from those described in the United States. Approximately half the cases were in women. Reported patients had no history of blood transfusion, homosexual activity or intravenous drug abuse.[16] Several cases were linked by heterosexual contact,[70] and a history of exposure to prostitutes was common.[16]

The sex ratio of cases in Africa is approximately 1:1.[16,75] Seroepidemiologic studies of healthy populations in Kinshasa show a bimodal age-specific curve with a first peak among infants (1% to 2% positive) and a second peak among adolescents and young adults (8%). The mean age of AIDS cases in Kinshasa is 34.[75]

In Zaire more male cases (50%) than control subjects (14%) have a history of sexually transmitted disease.[70] In Zaire, Rwanda and Zambia, patients are frequently from the middle or upper classes.[70,71,76] Additional case control studies have shown that AIDS patients have a significantly higher mean number of heterosexual partners than controls (32 versus 3) and that more male patients than controls have a history of sex with prostitutes (81% versus 34%).[16] These features, together with the absence of other identified risk factors, indicate that heterosexual transmission is the major form of HIV transmission in Africa.

Sequential serosurveys have defined a possible pattern of heterosexual spread of HIV in Africa. In traditional rural village areas, such as the Equator region of Zaire, the virus was present in 0.8% of inhabitants by 1976, and seroprevalence rates in 1986 remained stable at 0.8% (N. Nzilambi, K.M. De Cock, D.M. Forthal, et al, "Stability of the Prevalence of Infection With Human Immunodeficiency Virus Over 10 Years in Rural Zaire," submitted for publication, 1987). In urban areas, on the other hand, seroprevalence rates have risen as much as 1% per year[77] to levels of 6% to 9%.[67,75] Studies in African cities have shown that initial seropositive results are often documented in female prostitutes, especially those reporting contact with men from other HIV-endemic areas. After rates rise in prostitutes, seropositivity begins to increase among men who are patients in clinics for sexually transmitted diseases and subsequently appears in pregnant women attending prenatal clinics.[16,78-80]

As a consequence of heterosexual transmission and the prevelance of AIDS and other forms of HIV infection in women, perinatal transmission also plays a significant role in Africa. In a prospective study in Zaire, 5.6% of 2,400 mothers were HIV positive, and 45.9% of their infants had HIV immunoglobulin M antibodies. Women at a more advanced stage of HIV infection with lower T4 lymphocyte counts are more likely to deliver infected infants.[81]

Because of the high seroprevalence of HIV infection in some African countries and the fact that donor HIV screening is either nonexistent or has only been instituted recently, AIDS cases due to blood transfusions continue to be a problem. Studies in Zaire have shown a significant difference in a history of transfusion between seropositive and seronegative hospital workers: 9.3% versus 4.8%.[82] The high rate of HIV seropositivity among African children with sickle cell disease has been related to their total number of transfusions.[83]

Contaminated needles and syringes have been implicated in the spread of other blood-borne viral diseases in Africa,[84] and preliminary evidence suggests they play a role in the spread of HIV infection, as well. Because most AIDS patients have additional risk factors, the contribution of unsterile injections to disease spread is difficult to quantitate.

In a study of the postnatal acquisition of HIV infection in Kinshasa, seropositive children born to seronegative mothers had received a greater mean lifetime number of medical injections (immunizations not included) than control children (44 versus 23).[85] Nonmedical parenteral transmission from other skin-piercing procedures (ritual scarification, circumcision and others) may also play a role.[75,86]

Other retroviruses have recently been isolated from patients in Africa but at present appear to account for only a small number of AIDS cases. In West Africa, AIDS has been caused by a virus known as HIV-2.[87] Healthy HIV-2-seropositive persons have also been identified, and this virus is more prevalent than HIV-1 in West Africa. These HIV-2-seropositive persons fit an epidemiologic pattern suggesting sexual transmission.[87] A closely related virus known as human T-lympotropic virus type IV (HTLV-IV) has also been detected in West Africa.[88,89] Because HTLV-IV infection has been present since the mid 1970s in Senegal, however, and is not associated with immunologic abnormalities in prostitutes or increased seroprevalence among patients with tuberculosis or patients on infectious disease wards, its pathogenicity may be less than that of HIV strains.[88] A preliminary report has linked ten AIDS cases in Nigeria with another new retrovirus.[90]

Surveillance data reported to the World Health Organization indicate the present extent and growth of the epidemic in Africa. Reported AIDS cases have increased dramatically over the past two six-month intervals (986 to 2,073), but a major portion of this increase is due to improved surveillance. In all, 42 African countries report AIDS cases to WHO; 31 of these countries have reported a total of 4,585 cases (July 1987). The greatest number of cases has been reported from central, eastern and parts of southern Africa, with 12 countries reporting more than 100 cases each: Burundi, Central African Republic, the Congo, the Cote d'Ivoire, Ghana, Kenya, Rwanda, Tanzania, Uganda, Zaire, Zambia and Zimbabwe.

Oceania

As of July 1987, a total of 569 cases have been reported from Oceania; 523 of these are from Australia. The first case was reported from Australia in December 1982, and subsequent studies have shown a type I pattern of transmission.[91] The cumulative rate of 23.8 AIDS cases per million places Australia in the range of many western European nations but below that of the United States. Most cases have been reported from Sydney in New South Wales, with 83% of cases in homosexual or bisexual men and with a male-to-female sex ratio of 26:1.

Unlike other areas with a type I pattern of transmission, only 2% of cases occur in homosexual IV drug abusers and less than 1% in heterosexual IV drug abusers.[91] This may be due to the fact that needle sharing occurs only in small groups.[92] Only 1% of cases have been reported to be due to heterosexual contact.[91] Of the remaining cases from Oceania, 45 have been reported from New Zealand, which has an epidemiologic pattern similar to that of Australia.[93]

Other Countries

Transmission pattern III has been observed in other countries reporting small numbers of cases. Among 23 cases studied in Israel, 11 of 12 homosexual men were thought to have acquired infection abroad, and 8 hemophilia patients received imported commercial clotting factors.[94]

The first six cases of AIDS in Thailand were reported in homosexual or bisexual men, and 1985 seroprevalence studies showed rates of 0.8% to 2.4% among homosexual men and 0% among 2,880 female prostitutes and 309 heterosexual men.[95] Ten cases have been reported from the Philippines.

Only two AIDS cases have been reported from China, but seroprevalence has been reported to be 22% among hemophiliacs treated with factor VIII concentrates produced in the United States.[96] Japan has reported 43 AIDS cases, 40 in men and three in women. The male cases include 26 hemophiliacs (who received imported factor VIII and IX concentrates from the United States), 12 homosexuals (3 foreigners) and 2 others. Only one of the three women was Japanese, a prostitute from the Kobe area in the western part of Japan (H. Tamashiro, Y. Kawaguchi, M. Ito: "AIDS Prevention and Control in Japan," pp 719-722 in this issue).[97]

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Human Immunodeficiency Virus and Related Retroviruses

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This paper summarizes the current knowledge on the human immunodeficiency virus (HIV) and related retroviruses, describing basic characteristics of this new group of viruses such as morphologic and genetic structure, biological and cultural properties, virus growth characteristics, genetic variability and virus replication. The discovery of new human and simian retroviruses has prompted the World Health Organization (WHO) to convene a group of experts to establish criteria for their characterization. This will allow rapid identification of new variants that may arise and allow public health measures to be implemented accordingly. Different approaches are made to nomenclature in view of the evolution of knowledge about these viruses, and a system of nomenclature has been proposed by the WHO working group. This system, inspired by the one developed for the influenza viruses, is practical and descriptive, providing information on the origins of the organism and its type.

(Nájera R, Herrera MI, de Andrés R: Human immunodeficiency virus and related retroviruses, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:702-708)

Since it was endorsed by the International Committee on the Taxonomy of Viruses (ICTV), the name human immunodeficiency virus (HIV) has been adopted as the vernacular name, replacing the designations human T-lymphotropic virus type III (HTLV-III) and lymphadenopathy-associated virus (LAV).

The human retrovirus implicated as the agent causing the acquired immunodeficiency syndrome (AIDS) had been previously described by different authors under several designations, the first being that of the French group, which named it T-lymphotropic retrovirus,[1] followed by LAV,[2] HTLV-III,[3] immunodeficiency-associated virus,[4] AIDS-related virus (ARV)[5] and HTLV-III/LAV or LAV/HTLV-III. The last name was adopted by the World Health Organization (WHO) following the First International Conference on AIDS in Atlanta in 1985.

In May 1986, the committee recommended the name HIV to replace LAV/HTLV-III[6] in an attempt to unify the numerous previous designations of the virus, following the setting of criteria for establishing a uniform international nomenclature for viruses based on their taxonomy. According to the criteria, a retrovirus should be designated by a name having the following components: the species of the host from which the agent has been isolated, the major pathological property of the agent and the word "virus." This designation should be completed with a short name of the town (in parentheses) in which the isolation was made, in order to characterize it geographically, and an index allowing the identification of the individual viral organism.

By applying these criteria in naming HIV, the difference was established between this virus and HTLV-I and HTLV-II and any controversy avoided regarding priority of the discovery of the virus and emotive connections of the virus with the disease or its methods of transmission. However, as it was mentioned in a letter to *Science* by F. Brown, the president of ICTV, "Much still remains to be learned about the relationship of the human immunodeficiency virus with other retroviruses, and, therefore, designation of an international name would be premature."[6]

Therefore, it must be taken into account that the ICTV, as the official body of the Division of Virology of the International Union of Societies for Microbiology, has rules for virus nomenclature that should be followed before a name can be officially endorsed as international.[7] Thus, a new rule (No. 18) states that,

> The approval of the virus species proposed, species name and species type will be followed in two stages. In a first stage, a provisional approval can be obtained. These provisionally approved proposals will be published in an ICTV report. In a second stage, after a three-year interval, the proposals might obtain the final approval from the ICTV.

The apparent difficulties encountered and the care taken in taxonomy do not simply reflect questions of semantics, since the name of a virus contains, in a certain way, its essence. Thus, in a recent report from ICTV it is admitted that "The naming of virus species has lagged behind. It is first necessary to define what we mean by a virus species" and the proposal that "It should be defined as the smallest populations of viruses sharing a pool of genes maintained distinct from the gene pools of other viruses" has been vigorously debated.[8]

Classification of HIV

HIV is classified as belonging to the subfamily Lentivirinae according to its morphologic and morphogenetic characteristics, as it exhibits an electron dense cylindrical inner nucleoid. It is not tumorigenic or cell transforming in vitro, and its outer envelope glycoproteins show a progressive anti-

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ABBREVIATIONS USED IN TEXT

AGM = African green monkey
AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
ARV = AIDS-related virus
BLV = bovine leukemia virus
CAEV = caprine arthritis and encephalitis virus
EIAV = equine infectious anemia virus
HIV = human immunodeficiency virus
HTLV-III = human T-lymphotropic virus type III
IAV = immunodeficiency-associated virus
ICTV = International Committee on the Taxonomy of Viruses
LAV = lymphadenopathy-associated virus
mRNA = messenger RNA
SIV = simian immunodeficiency virus
STLV-III = simian T-lymphotropic virus type III
WHO = World Health Organization

genic drift. These characteristics coincide with those of the virus of visna disease in sheep and goats and of equine infectious anemia virus (EIAV) in horses. On the other hand, studies on the *pol* and *env* gene structure of different retroviruses also suggest the convenience of its classification among the lentiviruses.[9]

The group of lentiviruses could thus include HIV, EIAV, visna virus and caprine arthritis and encephalitis virus (CAEV), while other T-cell lymphotropic viruses such as HTLV-I and HTLV-II could be classified together with bovine leukemia virus (BLV) and possibly with simian T-cell lymphotropic virus (STLV) in a different group or family, the so-called E family or HTLV/BLV.

In Haase's 1986 review article on the pathogenesis of the lentivirus, the EIAV and AIDS viruses are also provisionally included in the lentivirus subfamily according to their pathogenic characteristics because they, too, cause slow infections and share other properties. These include cell fusion and other cytopathic effects in tissue culture, virion morphology, polypeptide composition, large envelope glycoproteins, shared antigenic determinants in the major structural protein *(gag)*, similar size and structure of their genomes and nucleotide and amino acid sequence homologies mainly confined to conserved regions of *gag-pol*.[10]

In that same year Gallo and his co-workers proposed a name and group that stressed the characteristic T-cell tropism of these viruses.[11] More recently, taking into account these and other characteristics, a new classification has been proposed. This would include HTLV-I, HTLV-II, HTLV-III, bovine leukemia virus, simian T-cell lymphotropic virus and some lentiviruses, such as visna. That new group has been named "type T retrovirus" by Haseltine and colleagues[12] on the basis that these retroviruses share a property that is not present in other retroviruses—a peculiar mechanism for replication, the transcriptional transactivation—which is the result of the expression of a unique gene called *x-lor* or *tat*. According to these authors, the most important differential characteristics of all these viruses could be their transactivating mechanism, which clearly sets them apart from all the other retroviruses. They favor the inclusion of all the viruses having that gene in a group—retrovirus type T—where all the different viruses could be identified by numbers: I, II, III and so forth.

The human immunodeficiency virus shares with the other two previously discovered human T-cell leukemia viruses the following properties:

- T-lymphocyte tropism, especially for T4.
- In vitro induction of giant, multinucleated cells.
- Mg^{++}-dependent reverse transcriptase.
- Three major "core" proteins present, with a relatively small but important p24.
- A p17 protein located in the NH_2 terminal end of the *gag* protein, as in HTLV-I and HTLV-II and opposite to other retroviruses that have a small phosphoprotein in between.
- Distant antigenic and genetic relationships.
- Presence of an extra gene, the *x-lor*.
- An open reading frame at the 3′ region whose transcript is 1.8 to 2.2 kb, messenger RNA (mRNA), coding for a p27 protein.
- The transactivating function, the long terminal repeat fragment and the presence of new kinds of regulatory elements for cells that are very likely functions of the p27 protein coded by the 2 kb RNA.
- A probable African origin.
- The presence of common antigenic epitopes such as the one located in p24 and others.

These same authors also point out the major differences in the genomes of these viruses, HTLV-I, HTLV-II and HTLV-III (HIV). Thus, it is mentioned that a close relationship between the viruses LAV and HTLV-I has been reported only by Barre-Sinoussi and co-workers[1] and Montagnier and colleagues,[2] discussing immunologic cross-reactivity or by Feorino and associates[13] reporting on the homology between nucleotide sequences.

In summary, the discovery of the human retroviruses HTLV-I and HTLV-II and subsequently of the retrovirus of AIDS has prompted a wealth of insight into these and other related viruses and brought a great amount of knowledge about their biological and biochemical characteristics.

All this new information might lead to a reclassification of the retroviruses. This need is important in itself, and it is an indicator of how the recent data available stress the different types of relationships existing between HIV and the adult T-cell leukemic retroviruses, HTLV-I and HTLV-II, on the one hand and some lentiviruses such as visna, CAEV, EAIV and BLV on the other.

In a recent meeting of the WHO Special Programme on AIDS Working Group on the characterization of HIV-related retroviruses, a system of nomenclature was proposed.[14] It was agreed that a practical and descriptive system that could provide information on the origins of the organism and its type would have considerable merit. Such a system could have the following components:

- The vernacular name of the virus: for example, HIV for organisms of human origin and simian immunodeficiency virus (SIV) for those of simian origin.
- An index for the serologic/genetic type of the virus (HIV-1, HIV-2, SIV-2) based on examination of the *env* glycoprotein components.
- In the case of viruses from nonhuman primates, the genus and species of the host from which the agent was isolated (*Macaca mulatta* for viruses from rhesus monkeys, for instance) should be specified.
- The country and laboratory in which the isolation was made.
- An index that allows identification of the individual virus—a strain number, for example.
- Year of isolation of the strain.

TABLE 1.—*HIV Seroprevalence in Spain—1986*

Group	No. Positive	%	No. Negative	%	Total
AIDS/ARC (suspect)	210	86.78	32	13.22	242
Intravenous drug abusers	331	63.05	194	36.95	525
Homosexual/bisexual men	29	12.83	197	87.17	226
Children born to seropositive mothers	46	86.79	7	13.21	51
Voluntary blood donors	43	0.05	86.571	99.95	86.614

AIDS = acquired immunodeficiency syndrome, ARC = AIDS-related complex, HIV = human immunodeficiency virus

- The country where the person or animal from whom the virus was isolated, if such information is available.

Examples of the use of this proposed nomenclature system for HIV/SIV strains are HIV-1/France, Pasteur/LAV BRU/83 (France); HIV-1/USA, NIH/HTLV-III B/83 (USA), HIV-I/Spain, Carlos III/MAJ/86 (Spain); HIV-2/France, Pasteur/LAV-2 MIR/85 (Guinea-Bissau).

HIV Characteristics

At the Cold Spring Harbor Workshop on AIDS held in 1983, R.C. Gallo proposed that AIDS was probably caused by a lymphotropic retrovirus, presumably related to the HTLVs.[15]

This hypothesis was based on epidemiologic evidence suggesting that the cause of AIDS was an infective agent and that it was transmitted by blood transfusions. It was thought it could be a virus because filtered blood products such as those used in the treatment of hemophilia patients were shown to transmit the disease. The target of that virus could be the helper/inducer T-lymphocytes subset (phenotype OKT4/Leu $3a^+$), as their number was markedly decreased in AIDS patients. The only known infective agents with similar characteristics were the viruses HTLV-I and HTLV-II. On the other hand, it was known that another retrovirus, the feline leukemia virus was able to cause a disease in cats very similar to AIDS.

From that moment on, a systematic search was begun for a human retrovirus in lymphocytes. That search was possible because long-term growth of T cells had been previously achieved by Morgan and co-workers, who discovered the T-cell growth factor or interleukin 2[16] and also because very sensitive techniques for detecting the presence of retroviruses in cell cultures had been developed.[17-19]

In 1983 investigators from the Institute Pasteur in Paris published a report of the isolation of a retrovirus—then named T-cell human lymphotropic virus and that cross-reacted with HTLV-I—after some modifications were made in the cell culture protocols (addition of anti-α-interferon). As the virus was cytolytic for T cells, the amount of virus available was very small. It was studied by electron microscopy, but its association with AIDS could not yet be shown. After exchanging reagents for HTLV-I and HTLV-II with workers from the National Cancer Institute in the United States, the difference between the new virus and HTLV-I and HTLV-II could finally be established.

Several viruses were isolated: from patients with the lymphadenopathy syndrome, the lymphadenopathy-associated virus (LAV); and from patients with AIDS, the immunodeficiency-associated virus (IAV). However, the French organisms, in general, are usually referred to as LAV.

Montagnier and colleagues first detected the presence of specific antibodies in only 20% of AIDS patients, a result that could be attributed to the lack of an efficient system for viral replication.[2,20] In 1984 the group from the National Cancer Institute published several reports in which the HTLV-III virus and its association with AIDS were described.[3,21-23] The development of a permanent T4-lymphocyte cell line that was permissive to the virus but at the same time partially resistant to its cytopathic effect made this possible. This cell line could be chronically infected and cultured. Continuous production of the virus was possible and the cultures were enduring. Mass production of HTLV-III allowed its concentration and purification, and further biochemical and seroepidemiologic studies could then be performed.

The cell line H9, which was selected from among several cell lines that had been developed, was a derivative of a T-cell leukemic cell line. It could be kept in the laboratory by serial passages and could be cultured in the presence of fetal bovine serum without interleukin 2 or anti-α-interferon, thus facilitating its handling.

Later that year a third group, Levy and co-workers, isolated another virus from AIDS patients that was designated as AIDS-associated retrovirus (ARV).[5]

It is widely accepted that all these viruses are the etiologic agents of AIDS. This is supported by seroepidemiologic studies showing a clear association between the presence of antibodies and AIDS or the AIDS-related complex (ARC). A great number of studies have shown the presence of antibodies in 100% of AIDS patients and in almost all the ARC patients. On the other hand, the antibodies were undetectable in the controls. The presence of antibodies is an indicator of the rate of infection in the different populations affected.

Table 1 summarizes some of the serologic data from studies in our laboratory.[24] It can be seen that all the AIDS patients have antibodies. The groups with higher rates of infection are the intravenous drug abusers, children born to infected mothers and, with a considerably lower rate, homosexual or bisexual men. A high rate of infection in intravenous drug abusers has also been reported in other Mediterranean countries.

Morphology and Ultrastructure

Early pictures of HIV taken with an electron microscope by Montagnier's group showed that the virus shared with HTLV-I and HTLV-II not only some of their biochemical and biological characteristics but also their main morphologic features. The virus appeared as a spherical or quasi-spherical particle, with a 100-nm mean diameter, an outer envelope studded with spikes and an inner core containing a dense eccentric inner nucleoid. These features were one of the clues that helped to classify HIV in the Retroviridae family, as it appeared similar to the viruses of the "type C oncovirus group." The asymmetrical localization of the inner nucleoid or "central core" of these viruses was also a morphologic characteristic of HTLV-I and HTLV-II. More detailed

morphologic studies, however, showed that this "central core" often displayed a tubular structure, a feature characteristic of the lentivirus subfamily (Figure 1).

Current knowledge of the HIV ultrastructure, supported by the work of Gelderblom and colleagues at the Robert Koch Institute in Berlin,[25] among others, shows that the virus's main morphologic features are the following:

- An outer envelope covered with knobs or spikes made up of the two envelope glycoproteins: gp 120, which is the outer spike component, and gp 41, which is attached to it and which sits in the viral lipidic membrane. It has been suggested that the distribution of gp 120 on the viral surface is similar to that of a soccer ball made of 12 pentagons and 20 hexagons stitched together to make a sphere. Gp 120 would be located at the corners of the hexagons, with an extra molecule at the center of each hexagon.
- An outer shell or core shell, which is composed of protein p17, arranged in an icosahedral structure and located at a very small distance from the outer envelope (unlike HTLV-I and HTLV-II).
- An inner nucleoid or central core made up of protein p 24 arranged in a helical pattern. In some pictures of the virus, this appears as a tubular structure, while in others this core is like a cone that is hollow, open at the narrow end (the top) and indented at the other end (the base).

As is characteristic for all the other retroviruses, the HIV structural components are assembled at the membrane of the cell it infects, in a process called "budding" (Figure 2).

It seems that the stages of this budding process are also different in HIV maturation from those described by Bernhard for type-C virus particles.[26] According to Gelderblom and associates, once the virus is released, shedding of gp 120 might occur, making it difficult for antibodies to stick to the free virus particles.[27] Further research on these subjects could also be of some help in classifying HIV in one subfamily or another.

The HIV envelope plays an important role in the specific cytopathic effect of HIV infection, syncytium formation and the like. The giant, multinucleated cells that appear in permissive cell cultures after infection are easy to detect by light microscopy and show a characteristic surface morphology when studied by scanning electron microscopy (Figure 3). These giant cells, which have been also observed in the brain by light microscopy and also appear in the blood of seropositive persons and AIDS patients (R. Nájera, MD, R. de Andres, MSc, I. Santa-Maria and M.I. Herrera, PhD, unpublished results, June 1986), could be a hallmark for this disease. However, a more precise characterization of infection by HIV should be achieved by means of specific immunolabeling of the cell. Immunofluorescence and immunoperoxidase techniques have been used, but the detection of the immune label by electron microscopy should prove to be more specific and sensitive. A technique that combines both the morphologic information and the rapid procedures of scanning electron microscopy with the precise antigen detection provided by the use of electron microscopy and immunolabeling with monoclonal antibodies has been recently applied to the detection of HIV antigens in infected cells by Herrera and co-workers.[28] A combination of high resolution scanning transmission electron microscopy and gold labeling techniques has been used to detect p 24, p 17 and gp 41 proteins in mononuclear cells from patients (Figure 4).

A wide variety of applications of this method to the study of AIDS, such as the early diagnosis, monitoring patients during antiviral therapy and others, can be expected.

Biological Properties

In vitro infection of human lymphocytes by HIV is characterized by a burst of virus production occurring one to three

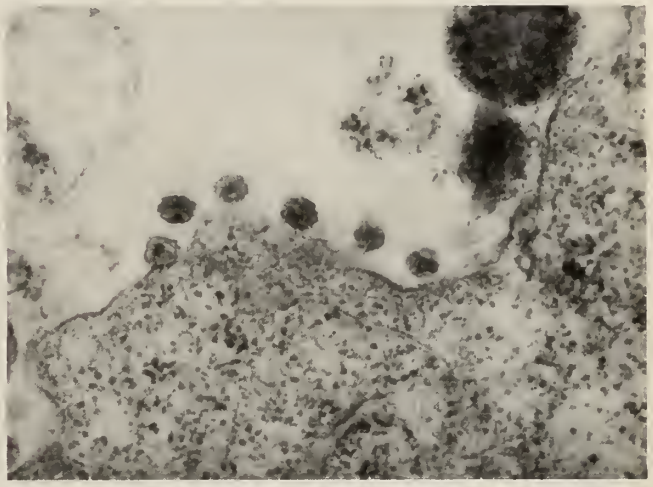

Figure 1.—The transmission electron micrograph shows human immunodeficiency virus particles invading a cell (× 72,000).

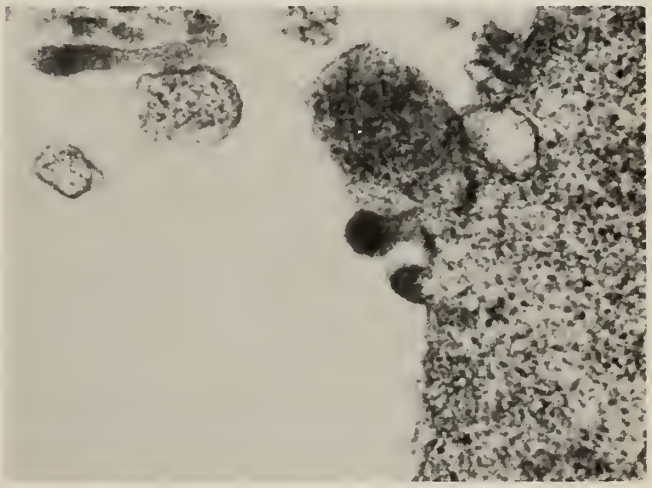

Figure 2.—The transmission electron microgram shows human immunodeficiency virus budding from a cell (× 155,000).

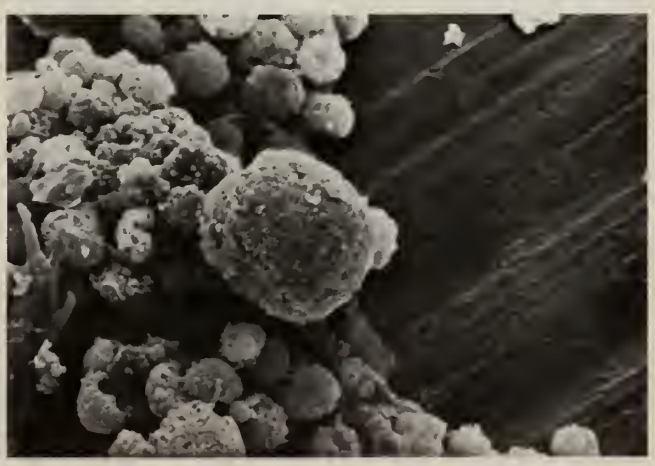

Figure 3.—The scanning electron micrograph shows a group of human immunodeficiency virus-infected cells, with a "giant" cell in the center (× 1,800).

weeks following infection. Within the heterogeneous population of T cells, T4 lymphocytes (phenotype OKT 4/Leu 3 a$^+$) are apparently infected, but it has been observed that other cell types, such as Epstein-Barr virus-transformed B lymphocytes, Langerhans' cells and macrophages, can also be infected. It has been reported recently that the major type of cell that can be productively infected with HIV in brain tissue is the mononuclear phagocyte, as suggested by the detection of budding virus particles and the long-term production of infectious virus in the primary cultures.[29] Virus particles have also been detected in astrocytes and microglial cells, however, but not in neurons, oligodendrocytes, pericytes or endothelial cells, though some damage to endothelial cells has been reported in children with AIDS having unusual basal ganglia calcification.[30]

Virus Isolation

The human immunodeficiency virus is generally cultured from specimens of peripheral blood from infected persons. The virus frequently has been identified in semen, lymph nodes and brain tissue and very seldom in saliva, sweat or bronchial exudates.

Mononuclear cells from peripheral blood are obtained after layering a specimen of heparinized venous blood over a Ficoll-Hypaque density gradient and centrifuging the specimen at 750 g for 20 minutes. The mononuclear cells are then collected, activated with phytohemagglutinin for two to three days and cultured in a medium supplemented with interleukin 2. The virus can be detected either with reverse transcriptase assays of the tissue culture fluid, by immunofluorescence or by electron microscopy for the presence of antigens in cells. Once isolated, the virus can be transmitted to other cells, mostly to umbilical cord blood lymphocytes or to permanent cell lines of T4 or macrophage origin.

The virus can be identified in 20% of symptomless seropositive individuals, in 50% of patients with AIDS and in 80% of the patients with ARC. The smaller percentage of organisms obtained from AIDS patients, when compared with the number of them from ARC patients at an earlier stage of the disease, could be explained by the specific cytopathic effect of this virus, as viral replication can also be cytotoxic, depending on the cell type.

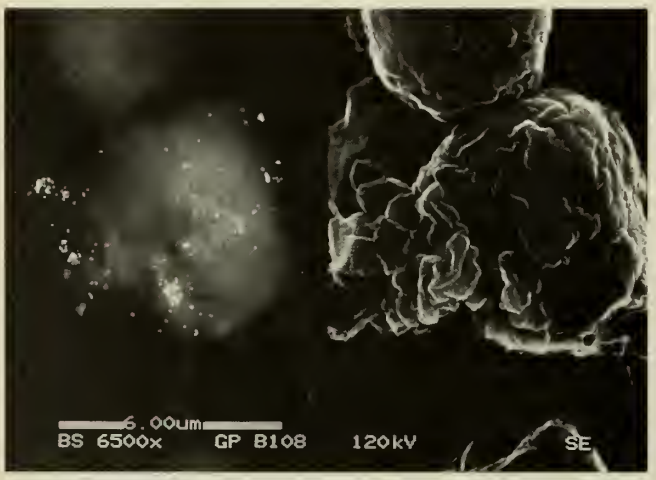

Figure 4.—The paired scanning/transmission electron micrograph of peripheral blood mononuclear cells from a patient seropositive for human immunodeficiency virus antibodies shows alterations in surface morphology (secondary electrons image) and gold-labeled antigens (backscattered electrons image) (× 6,500).

Cytopathic Effect

One effect of the infection of lymphocytes by HIV is the formation of multinucleated giant cells or syncytia that die out rapidly. Syncytial formation appears to result from the action of two antigens that are the products of the *env* gene of HIV, the proteins gp 160 and gp 120; gp 160 is considered to be a precursor of gp 120, the outer spike antigen. Infected cells express this antigen in their surface. As a result, they have a great avidity for binding to cells expressing the T4 phenotype (or permissive cells) and can serve to nucleate the formation of syncytia with them via a fusion reaction. This effect may help to explain the marked depletion of T4 lymphocytes observed in AIDS patients despite the small percentage of peripheral blood lymphocytes actively producing viral messages at any given time.[31]

The cytopathic effect can be clearly seen by light microscopy in fresh preparations, and for this reason it is used as an indicator of viral growth.

Genetic and Antigenic Components

The genome of HIV is similar to those of the other retroviruses, with three major structural genes, *gag, pol* and *env*, that are flanked by sequences repeated on both ends of the genome (5′ and 3′ terminals).

The *gag* gene codes for the group-specific proteins or group antigens. The *pol* gene codes for the polymerases, the enzymes required for viral replication, a reverse transcriptase and an endonuclease. The first one, the reverse transcriptase, which gives name to the retrovirus family, is an enzyme that transcribes the RNA genome into a DNA provirus, which then becomes integrated into the host chromosomal DNA. The *env* gene codes for the external envelope proteins of the virus that serve to bind the virus to the receptor of the permissive cells and that play a role in the neutralization of the virus.

However, the genome of HIV is much more complex than that of the other retroviruses, as it consists of eight genes encoding different proteins. The genome coding potential and protein processing in HIV are summarized in Table 2.

Genetic Variability

Since the studies on HIV began, its great variability has become apparent. LAV and HTLV-III differ in 1.5% of their sequences. However, the variations among other viruses are even greater: for example, ARV and RF-II show a 10% variation.

The recently isolated virus LAV-2[32] differs from the previous one (LAV-1) to such a great extent that it supports its classification as another subgroup. LAV-2 was isolated from two patients without antibodies against LAV-1. The genomic differences between LAV-1 and LAV-2 are estimated to be 30%. People infected with LAV-1 do not have antibodies against LAV-2 envelope proteins; however, serum from LAV-2-infected patients cross-reacts with LAV-1 core proteins.

Another virus, HTLV-IV, isolated from three healthy Senegalese, shows antigenic cross-reactivity and similar characteristics to a simian virus called STLV-III African green monkey (AGM) that was isolated from rhesus monkeys that were kept in captivity and had an AIDS-like illness. Further studies showed that this virus had infected 50% of asymptomatic wild African green monkeys. The Swedish group of Biberfeld has also isolated a virus (SBL-6669) serologically

TABLE 2.—*Human Immunodeficiency Virus Type 1 Genes and Gene Products*

Coding Gene	*Protein*
gag	p 24(p 25)*, p 17(p 18)*, p 15(p 13)* (group antigen) p 53-55 (precursor)
pol	p 66/p 51(p 68/p 53)* (reverse transcriptase) p 32-34 (endonuclease)
sor (Q)†	p 23
tat	p 14 (transactivator)
env	gp 120(gp 110)* gp 41 (envelope) gp 160 (precursor)
3'orf (F)†	p 27
trs (art)	p 16 (antirepressor)
R	—

*Alternative molecular weight values.
†Alternative gene designation.

related to the last two.[33] All of them share similarities in their *env* glycoprotein components.

The only difference existing between LAV-2 and HTLV-IV is that LAV-2 has been isolated from patients, while HTLV-IV has been found in healthy individuals. On the other hand, though both of them can infect permissive cells, the effect of LAV-2 is cytolytic, causing the cells to die, while HTLV-IV is able to infect cells but not kill them. The serologic data suggest that HTLV-IV shares antigenic epitopes with STLV-III AGM but not with the etiologic agent of AIDS—LAV/HTLV-III.[34]

Recently, Hahn and co-workers studied the genetic variation of the virus over time in the same patient.[35] The changes detected in the viruses obtained over a two-year period extended throughout the viral genomes and consisted of clustered and isolated nucleotide point mutations as well as short deletions or insertions. A comparative analysis indicated that the viruses had evolved from a common progenitor virus.

The rate of evolution was estimated to be at least 10^{-3} nucleotide substitutions per site per year for the *env* gene and 10^{-4} for the *gag* gene, in agreement with the data on variability found for other RNA viruses (one million-fold greater than for most DNA genomes).

This evolutive model may suggest that once infected with one AIDS virus, individuals are protected from infection with other genotypically different viruses. Some type of interference mechanism appears to prevent simultaneous infection, even in cases such as homosexual men who reported having more than a thousand different sexual partners.

Variations in the *env* gene are especially important, as this gene codes for the external proteins to which the specific antibodies should attach. It appears that some type of immunologic pressure is exerted, inducing the mutant selection.

The distribution of nucleotide substitutions and deletions or insertions is not uniform throughout the *env* gene. Instead, such changes are clustered in the exterior portion of the envelope glycoproteins and coincide with the regions that, based in their secondary structure, glycosylation pattern and hydrophilicity, represent predicted antigenic sites.[36]

This great genetic variation, with its corresponding effect on antigenicity, is perhaps the greatest problem encountered in developing a vaccine, a problem that is similar to that of the influenza viruses. A better understanding of the mechanism used by the virus to kill the T cell has been achieved, however, and it has been possible to develop laboratory variants whereby, through a deletion in the *env* gene, viruses with a reduced killing potential have been obtained.[37] These viruses could be used to develop a vaccine because the two functions, replication and cytotoxicity, would be separated in them. It appears that the latter is associated with a piece of the *env* gene product at its carboxyterminal.

HIV Replication

The human immunodeficiency virus is attached to the cell by an interaction of the envelope glycoproteins with the cellular receptor. Fusion of the viral envelope with the cell membrane occurs, and the inner core of the virus enters the infected cell. At this time, under the control of the reverse transcriptase, decapsidation takes place and the nucleic acid is released. Once the RNA is copied into a DNA provirus, this becomes integrated in the cellular DNA but, in contrast with other retroviruses, nonintegrated DNA may accumulate in the cytoplasm of chronically infected cells.

Integration of the DNA transcript as a provirus is essential for virus replication. From its integration site in the host chromosomal DNA, the virus completes its replication cycle by directing the transcription into the messenger RNAs. Some of them have been already identified: a 4.2-kb RNA could be the messenger for synthesizing *env* proteins and two 2.2- and 2.0-kb strands of RNA could be used to synthesize the products of the *tat* and *3'orf* genes.

However, HIV shows a new and complex pattern of replication. The virus is able to stimulate its own replication in the infected cell. This autostimulation would be mediated by a bipartite gene, the *tat* gene, together with another gene called *art* (also bipartite). This would express an antirepressor of translation, activating the functions of the *gag* and *env* genes and, in consequence, regulating the viral replication.

The virus remains in an infected person for a lifetime as a part of that person's genetic material integrated in the cellular DNA as a provirus. It may also be found in the cytoplasm as extrachromosomal DNA. Under stimulation, the lymphocyte replicates its DNA, and, simultaneously, the viral DNA is also replicated and infectious virus is produced.

Integrated viral DNA has been detected in tissue specimens from patients with AIDS or ARC. Viral expression has been frequently demonstrated in the lymph nodes, spleen, brain and peripheral blood from patients.

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Clinical Manifestations and the Natural History of HIV Infection in Adults

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The clinical expression of infection with the human immunodeficiency virus (HIV) appears increasingly complex. It includes manifestations due to opportunistic diseases, as well as illness directly caused by HIV itself. Neurologic disease may include involvement of the brain, spinal cord and peripheral nerves and is probably directly caused by HIV, as is lymphocytic interstitial pneumonia. The etiology of the chronic diarrhea and a papular pruritic skin eruption associated with HIV infection is unclear. Between 2% and 8% of HIV-infected persons progress to the acquired immunodeficiency syndrome (AIDS) per year, with no apparent decrease in the rate of disease progression over time. A chronically activated state secondary to chronic microbial antigenic exposure may increase both the susceptibility to HIV infection and development of disease. Increased HIV gene expression, followed by persistent antigenemia, appear to be triggering factors in clinical deterioration. The role, if any, of environmental and/or genetic cofactors remains unclear.

(Piot P, Colebunders R: Clinical manifestations and the natural history of HIV infection in adults, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:709-712)

The clinical expression of infection with the human immunodeficiency virus (HIV) appears increasingly complex. It includes manifestations due to opportunistic diseases, as well as illness directly caused by HIV itself. The types of opportunistic infections and neoplasms may vary not only in populations of different geographic origin but also according to the probable way the HIV infection was acquired.

HIV infection may be subdivided into at least four different stages; they are not necessarily present or consecutive events in all patients. These stages include acute illness, the latency phase, persistent generalized lymphadenopathy and AIDS-related complex and AIDS. A precise understanding of the natural history of HIV infection is essential not only for predicting the further course of the AIDS epidemic but also for the development and evaluation of interventions for the prevention and treatment of HIV infection and AIDS.

Clinical Manifestations

Definition of AIDS

The original definition of the acquired immunodeficiency syndrome for surveillance purposes required full documentation of specified opportunistic disease.[1] However, particularly since the widespread availability of HIV serology, a number of new clinical syndromes associated with HIV infection have been recognized. In addition, there has been a growing awareness that physicians may not always want to use often invasive procedures to document opportunistic diseases in patients with AIDS and that adequate diagnostic facilities for opportunistic infections may not be available in many geographic areas, including both industrialized and developing nations. For these reasons and to improve the sensitivity and specificity of the then-prevailing case definition, the Centers for Disease Control have adopted revised AIDS criteria.[2] The major changes in the case definition are the inclusion of HIV encephalopathy and dementia, HIV wasting syndrome and a broader range of specific diseases indicative of AIDS such as certain bacterial infections; the inclusion of AIDS patients whose indicator diseases are diagnosed presumptively, and the elimination of the requirement of the absence of other causes of immunodeficiency.

In 1985 a provisional clinical case definition of AIDS for Africa had already been proposed during a World Health Organization (WHO) Workshop on AIDS in Africa in Bangui, Central African Republic. This case definition was highly specific and moderately sensitive for HIV infection in Kinshasa, Zaire.[3]

Acute Phase

The human immunodeficiency virus disease may occur as early as one week after infection and usually precedes seroconversion, which commonly occurs between 6 and 12 weeks after infection but may take as long as 8 months.

Several studies have now described the clinical manifestations of early HIV disease. Fever, lymphadenopathy, night sweating, headache and cough were all significantly associated with seroconversion. One third to half of patients with seroconversion report at least one of these symptoms (Table 1).[4,5] Seroconversion may also be associated with severe illness, particularly acute encephalopathy.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ARC = AIDS-related complex
HIV = human immunodeficiency virus
PGL = persistent generalized lymphadenopathy
WHO = World Health Organization

Persistent Generalized Lymphadenopathy and AIDS-Related Complex

Persistent generalized lymphadenopathy (PGL) is defined when a patient with HIV infection has lymph nodes of greater than 1 cm in diameter involving two or more extrainguinal sites of at least three months' duration and in the absence of any current illness or drug use known to cause lymphadenopathy. About a third of patients with PGL are asymptomatic. Lymphadenopathy may slowly regress in size during the course of the disease. Systematic performance of lymph node biopsies in HIV-infected persons is not recommended but is indicated when lymph nodes are abnormally large, have an unusual consistency, when there is marked unilateral enlargement or in the presence of a fever of unknown origin.

Patients with AIDS-related complex (ARC) show symptoms, signs and immunologic defects similar to those of AIDS patients, but their symptoms and immunologic abnormalities are less severe. In contrast with AIDS patients, neither opportunistic infection nor malignant lesions can be diagnosed in ARC patients.

Signs and symptoms in ARC patients include weight loss, malaise, fatigue and lethargy, anorexia, abdominal discomfort, diarrhea, fever, night sweating, headache, itching, amenorrhea, lymphadenopathy and splenomegaly. These symptoms and signs are frequently intermittent. Weight loss is found in all patients and is generally progressive. Thrombocytopenia ($<50{,}000$ per μl) develops in approximately 10% of patients and is also often transient.

Many ARC patients have mucocutaneous lesions, and recognition of such skin manifestations can lead to an early diagnosis of AIDS or ARC. Skin manifestations include mainly varicella zoster, seborrheic dermatitis, recurrent and persistent orolabial and genital herpes, molluscum contagiosum, oral candidiasis and oral hairy leucoplakia. A generalized papular pruritic eruption (prurigo) is found in approximately 20% of African patients with HIV infection and frequently starts in an early stage of the disease. The cause is unknown.

Persistent diarrhea is one of the major complaints in patients with ARC or AIDS. Though intestinal parasites such as *Cryptosporidium* species and *Isospora belli* can be identified in 5% to 25% of HIV-infected patients with chronic diarrhea, in most patients no specific cause for the diarrhea is found.

AIDS

AIDS represents the most severe stage of the clinical spectrum of HIV infection. It is characterized by the presence of opportunistic infections and tumors as a result of a profound cellular immunodeficiency. The types of opportunistic infections depend largely on the past exposure of the host to microbial agents. This may explain the differences in frequency of certain opportunistic infections among African and American or European patients with AIDS.[6-11] Thus, *Pneumocystis carinii* pneumonia is by far the most common opportunistic infection in Americans and Europeans but is less frequently found in African patients. In contrast, the gastrointestinal system is a major site of infection in Africans with HIV disease, possibly because of a high exposure to enteric microbial agents. Table 2 shows the relative frequency of the most common opportunistic infections and of Kaposi's sarcoma.

The same signs and symptoms described for ARC patients occur in patients with AIDS but the manifestations become more pronounced. In addition, symptoms caused by opportunistic infections and malignant lesions are found. They will not be discussed here.

An increasing number of neurologic abnormalities are being documented in patients with HIV infections. These neurologic symptoms may be the initial manifestation of HIV disease and are often atypical in presentation. Prolonged headache in a person with HIV infection should always be an indication for a thorough neurologic investigation.

Central nervous system involvement may be directly due to HIV infection or to a variety of opportunistic infections. Neurologic disorders that are probably caused by HIV itself include encephalitis with progressive presenile dementia, acute and chronic meningitis, vacuolar myelopathy, peripheral neuropathy and polymyositis. Other causes of neurologic manifestations in patients with HIV infection include cryptococcal meningitis, cerebral toxoplasmosis, lymphoma of the brain, papovavirus infection, herpes simplex encephalitis,

TABLE 1.—*Clinical Manifestations of Early HIV Disease*

	% of Seroconverters With Symptom	
	*Fox and Co-workers** N=22	*Coutinho and Colleagues†* N=40
Pharyngitis	23	...
Coughing	...	25‡
Skin rash	14	15
Fatigue	23	17
Diarrhea	14	5
Fever	23‡	42‡
Lymphadenopathy	36‡	7.5
Night sweat	18‡	10
Headache	23‡	...
Nausea/vomiting	14	7.5

*From Fox, Eldred, Fuchs.[4]
†From Coutinho et al.[5]
‡$P<.05$ as compared to seronegative controls.

TABLE 2.—*Opportunistic Diseases in Different Patient Groups With AIDS**

	With Disease (%)				
		Haitians		Africans	
Opportunistic Disease	*Americans*	*USA*	*Haiti*	*Europe*	*Zaire*
Pneumocystis carinii pneumonia	61	42	20	25	17
Candidal esophagitis	10	51	67	23	17
Diarrhea >1 month					
with *Cryptosporidium*	3	3	5	9	6
with *Isospora belli*	NA	10	NA	4	1
Cryptococcosis	6	10	3	30	5
Herpetic ulceration >1 month	4	17	8	25	3
Cerebral toxoplasmosis	3	27	3	18	NA
Tuberculosis	NA	52	24	12	13
Atypical mycobacteria	4	4	NA	8	NA
Generalized CMV infection	5	13	10	25	NA
Progressive multifocal leukoencephalitis	0.6	1	NA	2	NA
Kaposi's sarcoma	26	12	26	21	4

CMV=cytomegalovirus, NA=not available

*Data from Peterman,[6] Pitchenik,[7] Pape,[8] Sonnet,[9] Colebunders,[10] Katlama,[11] et al.

TABLE 3.—*Development of AIDS in HIV-Antibody-Positive Adults in Selected Studies*

Patient Category	*Location*	*Investigators*	*No. Studied*	*Months of Follow up (mean or median)*	*No. of AIDS Cases per 100 Persons per Year*
Homosexual men	San Francisco	Hessal and co-workers[17]	63	72	5.0
	New York City	Polk and others[19]	165	18	4.0
	Multicenter AIDS Cohort Study, USA	Polk and others[19]	1,835	15	2.6
	London, UK	Weber and colleagues[20]	33	36	4.0
	Amsterdam, The Netherlands	De Wolf et al[21]	198	21	4.3
IV drug abusers	Queens, NY	Goedert and co-workers[22]	24	36	1.4
	Bronx, NY	Selwyn et al[23]	163	15	3.9
Blood recipients	USA	Ward and others[24]	54	46	2.4
Hemophiliacs	Hershey, Pa	Goedert and co-workers[22]	40	36	4.2
Heterosexual men and women	Nairobi, Kenya	Plummer and colleagues[25]	535	12	5.7
	Kinshasa, Zaire	Ngaly and others[26]	44	24	2.3

IV=intravenous

infection with cytomegalovirus, tuberculous and candidal meningitis and abscesses.

The most common neurologic disorder is a subacute encephalopathy characterized by progressive behavior changes associated with dementia. This "AIDS encephalopathy" or "AIDS dementia" occurs in approximately one third of AIDS patients. The onset is usually insidious, and cognitive dysfunction predominates initially. Common early motor signs include tremor and slowness, and the course is usually progressive towards severe dementia. Mutism, incontinence and paraplegia may develop in the end stage. A mild pleocytosis, an increased protein concentration and a low glucose concentration are often found upon examination of the cerebrospinal fluid.

Natural History of HIV Infection

Acquisition of Infection by Sexual Intercourse

HIV has now been isolated from virtually all bodily secretions and excretions that have been cultured, but there is no firm evidence as yet that body fluids other than blood, semen, cervicovaginal secretions and perhaps breast milk can transmit the virus. It has still not been unequivocally established in which form HIV is transmitted. However, other animal lentiviruses are transmitted via cell-bound virus inside monocytes and macrophages, and this is probably also the case with HIV. It also appears that HIV can only be isolated from semen, saliva and cervical secretions containing cells and not from cell-free filtrates, suggesting that HIV is cell bound in these secretions.

Though the present data on factors enhancing sexual transmission of HIV are incomplete, some patterns are emerging from studies in both homosexual men and heterosexuals. Genital trauma clearly facilitates sexual transmission of HIV. Thus, it has now been well established in several studies that receptive anal intercourse is the major risk factor for HIV acquisition in gay men. In addition, rectal bleeding during or after intercourse and the use of an enema or douche before sex are risk factors for HIV infection in homosexual men. Similarly, among female prostitutes in Zaire, introducing products or objects into the vagina was associated with HIV seropositivity.[12] Finally, studies in Africa have suggested that genital ulcers are significant risk factors for heterosexual acquisition of HIV.[13] If transmission of HIV infection is more efficient in the presence of genital ulcerations, control of sexually transmitted diseases may play an important role in the indirect control of the spread of HIV infection in some populations.

A second major factor determining infectivity appears to be the stage of infection, probably because of a higher virus expression associated with disease progression. Thus, a female sex partner of an HIV-infected hemophiliac was more likely to be infected when her partner had a low concentration of T helper cells.[14] Such an association between infectivity and duration of infection and low CD 4^+ cell counts was also observed in studies on congenital transmission of HIV infection in Africa.[15,16]

Progression of Disease

After a variable period of time some persons progress to HIV-related disease. Table 3 gives annual progression rates to AIDS in seropositive adults belonging to five different patient categories, showing that per year AIDS develops in approximately 2% to 5% of HIV-infected persons, regardless, apparently, of the route of infection or the life-style.[17-26] In the San Francisco cohort of gay men, which has had the longest observation time, 35% of seropositive men progressed to AIDS nearly seven years after the infection.[18] Patients with PGL or ARC are at increased risk for AIDS, with annual progression rates to AIDS of 6% to 20%. The risk for AIDS apparently does not decrease with the duration of infection.

Why does AIDS develop in some infected persons within five years while others remain healthy? This is a basic question in many infectious diseases, and we tend to forget that the answer is unknown for virtually all.

The respective ongoing cohort studies have come up with a spectrum of risk factors for the development of AIDS. A consistent predictor of clinical deterioration is a low concentration of T helper lymphocytes (OKT 4^+, CD 4^+, Leu $3a^+$ cells). Thus, in one study in Los Angeles, 5% of gay men who had ≥ 500 CD 4^+ cells per μl at enrollment in a study progressed to AIDS, as compared with 50% of men with less than 100 such cells per μl.[27] Additional indicators suggesting a poor prognosis include oral candidiasis, lymphopenia, an increased erythrocyte sedimentation rate, hemoglobin levels below 13 grams per dl, decreased antigen-stimulated lymphocyte proliferation, reduced gamma interferon generation, impairment of the specific cellular response to HIV and the presence of antilymphocyte antibodies.

Investigators in Europe have now documented a specific loss of IgG antibodies against the *gag* gene products of HIV

during clinical progression of HIV infection. Both the prevalence and the concentration of antibodies to the p24 core protein are decreased among patients with AIDS, as compared with asymptomatic HIV-seropositive men.[20,28] In contrast, antibody against the viral envelope glycoprotein remains stable throughout the course of disease. Loss of antibody inhibitor to reverse transcriptase activity appears also to precede the development of AIDS.[29]

The decline in anti-p24 antibodies is probably secondary to increased viral expression. Lange and Goudsmit showed that the decrease in antibody reactivity to the major HIV core protein is due to clearance of these antibodies by excessively produced viral antigen, as evidenced by studies on circulating immune complexes.[30] A drastic decrease of CD 4^+ lymphocytes accompanying a significant increase of free viral antigen concentration seems to be the initial event in clinical deterioration.[21]

Prospective studies suggest the following pattern for free HIV antigen and antibody to p24: After an initial antigenemia preceding seroconversion, there is a variable period without detectable free HIV antigen (however, HIV can still be demonstrated in the T-helper lymphocytes); when anti-p24 antibodies decline, the free viral antigen becomes detectable again, which may herald the onset of AIDS.[10,21,28,30] Individuals with persistent antigenemia following infection are at a significantly increased risk for AIDS.

A reasonable conclusion from several studies is that the primary pathogenic mechanism in serious HIV disease appears to be enhanced expression of viral genes following lymphocyte activation. There is some experimental support for a role of cofactors in the replication and dissemination of HIV. Thus, proliferating CD 4^+ cells are more susceptible to productive infection with HIV in vitro than nonproliferating cells; mononuclear cells activated by tetanus toxoid are 10 to 100 times more susceptible to viral replication[31]; coinfection of cells by HIV and DNA viruses such as herpes simplex and varicella zoster can reactivate transcription of latent HIV by *tat*-like protein. These data suggest that both soluble antigen and DNA viruses may also serve as cofactors in vivo in the development of clinical AIDS. This hypothesis is supported by the observation by Weber and colleagues that interfering sexually transmitted diseases may precipitate clinical deterioration in HIV-seropositive gay men.[32] The data on cofactors are still inconclusive, however, and epidemiologic studies on the role of other infectious diseases are extremely complex. This is also true about the role of other environmental factors such as amyl nitrite use, which has been linked to Kaposi's sarcoma.

An alternative model for the pathogenesis of clinical AIDS is a more direct role for the infecting HIV virus itself. Quantitative differences in in vitro virulence for cells have been reported and correlated with clinical severity of the infection, suggesting the existence of differences in pathogenicity among HIV strains.[33]

Finally, genetic factors in the host may determine both susceptibility to infection and clinical progression patterns. Both group-specific component and different HLA antigens have been implicated in disease expression.[34,35] All these findings require confirmation among persons of diverse geographic and ethnic backgrounds.

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Social, Cultural and Demographic Aspects of AIDS

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Both on national and international levels, the acquired immunodeficiency syndrome (AIDS) represents a formidable challenge to social institutions and to cultural assumptions. Its effect thus far, in what must be considered the very early stages of a protracted and unprecedented epidemic, has been to exacerbate existing social tensions and divisions over a surprisingly wide field. Though international leadership by the World Health Organization has been met with an unusually high degree of multinational cooperation, AIDS has also stimulated a degree of xenophobia and racial friction that, if allowed to grow, could handicap global AIDS control and prevention efforts.

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If there is an intellectually acceptable way of characterizing the social and cultural impact that the acquired immunodeficiency syndrome (AIDS) has had in the seven years since it was first diagnosed, it may be to say that this disease has exhibited an unusual propensity to exacerbate existing tensions within the body politic. Simultaneously, AIDS has inspired some impressive feats of community and international cooperation, among them the epidemiologic detective work that first uncovered the disease; the organization of the American homosexual community to meet the crisis in its ranks; the outstanding efforts on the part of a number of the world's low and medium income countries to develop national AIDS control strategies in the face of severe resource shortages, and the creation and operation by the World Health Organization (WHO) of its Special Programme on AIDS, making it the widely acknowledged leader in the field of international AIDS prevention and control.

AIDS and Social Divisiveness

To say that AIDS accentuates social divisions may at first seem to state the obvious, but an attempt to list instances of this phenomenon soon reveals that they are both more numerous and more wide-ranging than might initially have been supposed. Erroneously perceived at first as a specifically gay disease, AIDS has triggered a homophobic backlash that at its violent worst is manifested in episodes of AIDS-related attacks ("gay bashing") such as have been reported recently in the United States, Europe, Brazil and Mexico. Gay organizations, with some supporting statistical evidence, believe that such attacks are increasing and are likely to continue to do so. Prostitutes, too, have been the object of discriminatory and sometimes violent attention. Data from serologic studies on groups of prostitutes in African countries and elsewhere have revealed high and fast-rising rates of seropositivity, with the result that these prostitutes have tended to be seen more as a source of infection with the human immunodeficiency virus (HIV) than as a group particularly vulnerable to it. They have also been seen as a source of bad publicity by governments anxious to downplay the presence of AIDS in their countries. Whether in India, Kenya or the United States, the jailing of prostitutes has more accurately reflected the contempt of society for a marginal group than sound policies for arresting the spread of HIV. At least two murders of streetwalkers in Britain are believed to have been AIDS-related revenge killings.

As infection spreads, the polarization within society between those who are carriers of the virus and those who are not will increase. In June 1987 in Washington, DC, the growing antagonism between the two camps was made audibly evident during speeches dealing with the Reagan administration's views on selective mandatory testing. The President was booed and hissed at a fundraiser; Vice President Bush and Health Secretary Bowen received the same treatment as they addressed the Third International Conference on AIDS. Whatever other effects it produces, mandatory testing defines a class of HIV-carrying people whose legal rights and social prospects are thereby jeopardized.

This is equally true in the Third World, where hints of what is in store are already emerging. African students studying abroad on scholarships have been subjected to compulsory blood tests in several countries, including Belgium, West Germany, China and India. Those found to be carrying the virus have been summarily sent home to an uncertain future. African countries may decide to initiate their own screening programs for students before they go away, to save the ignominy and expense of having them rejected abroad. A seropositive student bright enough to secure a scholarship may now have few career prospects and be tormented by uncertainty about the risk of the development of the full-blown disease.

It remains to be seen whether the growing numbers of people shown to be virus carriers through both mandatory and

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
WHO = World Health Organization

voluntary testing schemes will be harbored humanely within their societies or increasingly victimized as plague carriers. At the present time there appears to be a precarious balance between the two reactions, but as the number of AIDS cases continues to rise inexorably (as it must—at least until the infections already contracted are fed through the epidemiologic curve), victimization seems likely to increase.

AIDS and Sexual Mores

The reevaluation of sexual mores that has been provoked by AIDS highlights another social debate, which in the West might be characterized as the argument between those who believe that sex can be made safe and those who believe that "to condom is to condone." That religion enters into this quarrel makes it all the more acrimonious; that it bears on the content of AIDS education programs for the younger generation makes it all the more acute.

The battleground in African and Asian countries may be quite different. There, sexual behaviors rooted in tribal traditions may prove to be obstacles to AIDS control in cultures where marital fidelity must be viewed outside the Judeo-Christian model of monogamy. For example, according to Zambian tradition, when a man dies his male relatives must have sex with his widow to cleanse from her the ghost of her husband. Among senior women (who can wield considerable influence) there is a strong resistance to any move to eradicate this practice. Though eradication would reduce the risk of HIV transmission, it would also, they feel, reduce the opportunity for widows to remarry and thus the material prospects of both widows and their children. To complicate matters, those who argue for changes in tradition to avert the spread of HIV may be tagged as having been "Westernized"—that is, having become alienated from their heritage as Africans and members of their tribe. Worldwide, what starts with sex ends in a complex of emotive religious and cultural issues that may take generations to untangle. Where the family (in the West) or the clan (in Africa and Asia) feels threatened as a fundamental social institution, AIDS control is likely to become more difficult.

Another sort of conflict in the field of biomedical research was dramatically illustrated by the dispute over the discovery of the AIDS virus between the rival laboratories of Robert Gallo and Luc Montagnier. Well covered in the media, the dispute became common knowledge even among segments of the public normally impervious to such issues and may have promoted a degree of cynicism about the value of scientific research in an economic climate where such research has been under fire.

A new dispute, over the potential therapeutic value of peptide T, has subsequently received substantial press coverage. The extent to which such issues may diminish public confidence in AIDS research is unclear, but their importance in this regard, particularly when two decades of investment in cancer research are now under heavy attack, should not be underestimated.

The production of an AIDS vaccine and its shepherding through all phases of clinical trials will require a high degree of public trust in the scientific community. Scientific controversies that tend to erode that trust must therefore be regarded as matters of serious concern.

AIDS is a propagandist's dream come true. Whether for a politician courting the support of an electorate tilted toward religious fundamentalism, a research scientist seeking funding for a large laboratory, a journalist looking for a big story or a parent trying to keep the children on the straight and narrow, the mention of AIDS is a trigger that generates an unusually complex array of social responses. Given the present incomplete state of knowledge about the acquired immunodeficiency syndrome—about the origins and the extent of spread of HIV, the dynamics and exact mode of its transmission, the natural history of the disease, the opportunities for therapeutic intervention and the psychological effects of infection—there exists a vast arena in which discourse on AIDS can take place free of the hazard of bumping into too many inconvenient facts. The social experience of infectious disease is founded on memories of past epidemics, and there are few, if any, historical parallels to the AIDS pandemic to which we can refer in the search for models of understanding and response. But there is a diagnostic test for exposure to HIV, and so the reflex human response to pestilence—to build a wall around the city—has become translated into the exercise of excluding presumably dangerous foreigners by screening their blood before they are allowed to enter the country. More than a dozen countries have decided to adopt such screening as a control measure, in spite of its obvious deficiencies: cost, inconvenience and failure to detect those whose exposure to the virus is very recent. The World Health Organization's advice—that screening of travelers is epidemiologically ineffective and diverts resources from measures more likely to prevent new infections—has been widely ignored.

Screening Practices

From the point of view of infection control, absurdities have resulted. One Austrian city screens foreigners requiring work permits, though nationals who may have contracted HIV in another part of Austria are not tested. Belgium screens students receiving state scholarships; are non-scholarship students considered less likely to have been exposed to the virus? Cuba screens nationals returning from AIDS-endemic regions and all foreigners except tourists—the hard currency that accompanies tourists presumably exerts a prophylactic effect with regard to the spread of HIV. Finland will soon screen all foreign students, though not its own students, who may have been exposed to the virus in the very countries from which the foreign students originate. In the West German state of Bavaria, resident foreigners, unless they come from a country that is a member of the European Community, must prove that they are HIV-negative. The fact that neighboring Belgium and France have very high numbers of AIDS cases per capita appears not to matter. India screens all foreign students and foreigners who wish to stay longer than one year except journalists. Kuwait, Saudi Arabia and the United Arab Emirates screen foreign workers, the Philippines screens long-term foreign residents and Iraq apparently screens everyone entering the country.

The United States, with more AIDS cases than have been reported from all other countries combined, will soon screen those foreigners who apply to immigrate there. Like the other politicians who enacted legislation to put screening of for-

eigners in force, President Reagan had available to him expert information that could easily have made plain the ineffectual nature of such measures in halting the global spread of AIDS. Like other politicians, he justified his decision in favor of mandatory screening as a step that was necessary to stem the advance of the disease. In doing so he, like other policy makers in favor of screening foreigners, was responding to a deeply felt social need to feel that barriers against AIDS can be erected that will make it easy to distinguish between the places where the virus is and the places where it is not. It is not surprising that people respond to a new and little understood danger by seeking a place of safety, a vantage point from which to observe and gauge the severity of the threat. What is unfortunate is that with AIDS, the sheer inappropriateness of this response is likely to provide the false sense of security that will lead to new and unnecessary HIV infections.

Placing the 'Blame'

Almost universally (and futilely) the social response to the appearance of HIV has been to try to locate the source of the epidemic in another country, culture or race. In the early stages of the American epidemic the classification of homosexuals and Haitian nationals as risk groups gave credence to this tendency. The efforts of American researchers to locate the origins of the AIDS virus in west or central Africa have lent impetus to the popular Western belief that the AIDS pandemic must have started somewhere on the "dark continent." It is no accident that African students were the first and selective targets of the mandatory screening measures that many countries have implemented. The link between AIDS and Africa now seems to be indelibly imprinted on the public mind, at least in the Western hemisphere.

You might, for example, in planning an African holiday, pick up a copy of the *1987 Fodor's Guide to Kenya*. There, as part of a generally helpful section on AIDS, you would find the statement that "Doctors speculate that in some African countries the infection rate may be 30% of the total population." There are no data to support such an assertion from any of the AIDS-affected African countries, least of all from Kenya, where at present serologic testing confined mainly to high-risk groups suggests that the current prevalence of HIV in the general population may be 1% or less. Many Africans fear that such inaccurate statements may create a climate in which tourism and other forms of commerce and exchange are blighted and in which discrimination against Africans is fueled. That African students abroad have already been victimized confirms that their fears may be well founded.

That the AIDS picture may look very different from the African or Asian perspective is a fact that Western societies have largely chosen to ignore. In a number of African countries the media have vociferously denounced Western researchers and journalists whose statements proposed Africa as the point of origin of HIV. Throughout most of Africa and Asia the common view is that the AIDS pandemic began with American homosexuals and was spread around the world by American travelers and imported American blood products. Anecdotal information illustrates this perspective. Recently, in Nairobi, a female Kenyan colleague walked down a main street with a visiting male British journalist. A friend of the Kenyan who saw them shouted out jokingly in Swahili: "Watch out—you'll get AIDS!" In the Philippines, a woman's group called Gabriella is trying to organize a lawsuit against the United States military. In their view, the 44 female prostitutes who have recently tested positive for HIV antibodies have been infected by servicemen clients from the American naval base at Subic Bay.

Anti-Western sentiment is not restricted to the person in the street. Noboru Takeshita, Japan's new prime minister, told this joke at a political fundraiser: Because of the soaring value of the Japanese yen, he said, American servicemen can no longer afford to go out with Japanese hospitality girls. Instead, they are staying on base giving AIDS to each other.

A short time ago in London, a group of two dozen experienced but nonmedical journalists from Asia, Africa and Latin America gathered for a seminar at the British Broadcasting Corporation. When they were asked informally how the AIDS pandemic got started, they responded with what they regarded as the accepted view: AIDS started in the United States and was carried to their countries mainly by Americans traveling abroad.

It is important to recognize that wherever people feel that they can assign blame for the spread of HIV to a defined cultural or racial group other than their own, they tend to feel that they have gained some measure of protection from infection. Among ethnic minority groups in New York City, for example, there has been a strong denial—despite the evidence that blacks and Latinos are currently contracting HIV at a faster rate than whites—that the disease they view as quintessentially the result of the "white man's vice" (homosexuality) could have invaded their community.

Racially or culturally based views about the transmission of HIV may in the long run be more difficult to erase and more obstructive of infection prevention than the other common type of misunderstanding—that one can "catch AIDS" through casual contact. It is much easier, on finding that the virus is among us, to blame an outsider than it is to blame a toilet seat or a beer glass. Thus, an observable impact of AIDS has been to sharpen existing social and racial divisions both within and between nations. While it has frequently been remarked that the chief cultural impact of AIDS will be the questioning of sexual mores and the more stringent social regulation of sexual behavior, AIDS has the potential of igniting intergroup enmity and conflict that may prove to be more profound.

A New World With AIDS—Health Promotion as a Catalyst for Change

ANTHONY J. MEYER, PhD, *Geneva*

Preventing the acquired immunodeficiency syndrome (AIDS) requires an unprecedented response from public health professionals, particularly educators and communicators involved with health promotion. Health promotion is defined and discussed in the light of recent experience in a broad range of public health programs. Increased sophistication is needed in the application of social science within health promotion and increased facility in mobilizing cross-sectorial resources to achieve public health objectives and generate confidence in approaching AIDS prevention.

(Meyer AJ: A new world with AIDS—Health promotion as a catalyst for change, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:716-718)

The face of the acquired immunodeficiency syndrome (AIDS) is global; we can recognize most of our countries there. As of November 1987, a total of 127 countries representing all continents officially reported 62,811 AIDS cases to the World Health Organization (WHO).[1] An estimated 5 to 10 million additional persons are infected with the human immunodeficiency virus (HIV).

Societal Ramifications

The economic and social consequences of AIDS are only now beginning to be understood. Data from surveys in New York City, Philadelphia and San Francisco suggest that the first 10,000 patients with AIDS reported in the United States will require an estimated 1.6 million days in hospital, resulting in over $1.4 billion in expenditures. An additional $4.8 billion in losses will be incurred for the 8,387 years of lost work from the disability and premature death of these patients.[2]

In many countries child survival may be adversely affected as children are infected in utero, through transfusions of contaminated blood or by the use of unsterile needles and syringes.

As HIV infection spreads through the urban areas of the world's least affluent countries, the gains in the development of human resources made in the past 20 years may be seriously eroded.

Disruption and disintegration of families and relationships, along with the loss of highly creative and skilled individuals to the economic and cultural well-being of society, represent a magnitude and quality of loss that we do not yet know how to fully describe or evaluate. We are in the presence of a pandemic that combines all of the historic and existential characteristics conveyed by the concept of "plague."

Societal Response

AIDS is gradually evoking a global response. Expressions of denial, fear and blame contend with expressions of coping, personal responsibility and caring. Out of and because of the human struggle engendered by AIDS, new symbols are emerging around us. Images and metaphors relating to sexual behavior, drug use and medical care startle us, arouse our concern and confront our assumptions and sensibilities. AIDS is changing how we talk to one another and what we are permitted to say.

Society at large is confronted with psychosocial disruption and its concomitant symbols, causing frank questions and discussions in families, classrooms, civic groups and churches and presenting a challenge to the limits of what our cultures and subcultures are willing to permit in the struggle to contain AIDS. The issues raised by the effort to control and prevent AIDS go far beyond the communication of information to improve knowledge. AIDS takes the measure of our sexual balance, our prejudices and our integrity, how we love and how we deal with death and dying.

Control of Epidemic

Thus, the task that AIDS requires of public health professionals, particularly educators and communicators involved with health promotion, is ambitious and probably unprecedented:

- *Setting the public agenda* to place AIDS prevention high on the list of public health priorities for health and education systems in the workplace, among friends and in the home. It must be permissible for everyone to talk about AIDS.
- *Informing the public,* particularly those in greatest need, about a broad range of basic AIDS facts in the context of

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
WHO = World Health Organization

local languages and cultures where the drama of AIDS prevention is played.

• *Generating appropriate concern* for self and others while reducing fearful and stigmatizing behavior.

• *Motivating the appropriate use* of health and education systems services, particularly among persons at greatest risk.

• *Supporting the adoption of preventive practices* along with their enabling skills, such as the ability to discuss sexual practices or the instruction of teachers in discussing AIDS in the classroom.

• *Establishing public support* for institutional responses helpful to the control and prevention of AIDS.

• *Serving as catalyst* for the evolution of a socially supportive environment for widespread change in well-established, often intimate and sometimes addictive practices.

Health Promotion Programs

It is not known how completely or how successfully health promotion programs will be able to implement this agenda. The WHO Special Programme on AIDS is cautiously optimistic. As of September 1987 it had assisted 57 countries in drafting national AIDS prevention and control plans. Each plan includes an extensive health promotion component, laying the foundation for the design, implementation and evaluation of programs for the general public and for targeted segments of that general public, including health care workers. Each plan must take advantage of every available means of communication —medical and interpersonal—in as many institutional settings as is reasonable, including counseling systems, education systems, programs in the workplace and programs generated by civic, religious and humanitarian interest groups. Two complementary trends within health promotion over the past two decades generate some confidence in the potential for success of this combination of well-designed, targeted interventions with broad, multifaceted national plans:

1. Increased sophistication in the application of social sciences in the design and implementation of programs aimed at modifying or establishing specific health practices; and
2. Increased facility in mobilizing cross-sectorial resources to achieve public health objectives.

In the context of AIDS prevention and control, health promotion can be broadly defined as the systematic attempt to influence positively specific health practices of large populations, using principles and methods of mass communication, instructional design, health education, social marketing, behavioral analysis, anthropology and related public health and social sciences. The term implies reliance on multiple channels and institutional resources coordinated to introduce sustained change in specific practices crucial to achieving a public health impact.

Methodology

Health promotion programs have progressed dramatically from the days when health education was associated exclusively with treatment at a clinic. Coverage and impact have increased through wider implementation:

TABLE 1.—*Decrease in Adult Smokers in United States*

Currently Smoking	*1964, %*	*1984, %*
All adults*	42	33
Men	52	35
Women	34	30

*85% of all smokers would like to quit.

• Multiple channels of communication are mobilized to reinforce messages and activities from a single program perspective;

• Information about specific behavior and its cultural and social context, in combination with principles and methods drawn from the social sciences, increasingly guides the communication strategy and message development process;

• Formative evaluation and ongoing monitoring improve program performance; and

• The power of face-to-face communication and traditional networks of training and communication are combined with the coverage, convenience and reinforcement of mass media.

Successful experience with well-designed and implemented programs for heart disease prevention, cancer prevention, diarrheal disease control, immunizations, clean water and sanitation, and family planning communication support the introduction of these more complex health promotion approaches. Significant positive change in health practices can be achieved.

Successful Model

The reduction of adult cigarette smoking in the United States provides a useful analogy for AIDS prevention, combining as it does carefully designed interventions with widespread public reaction and mobilization. Data on smoking habits in the United States show a significant and steady decline, representing change among millions of individuals (Table 1).[3]

We now know that the eventual positive trend in smoking cessation data cannot be explained by the dramatic success of a single, deliberately engineered health promotion intervention. Rather, it seems that numerous efforts over extended periods of time combined to achieve these results:

- Advice from physicians and health workers;
- Public service messages portraying smoking as antisocial behavior;
- Changes in city and county ordinances for restaurants and other public places;
- Tightening of airline smoking regulations;
- Proliferation of smoking cessation clinics, and
- Antismoking education in public schools.

The net effect of this process was the activation over time of all systems of communication—mass media and interpersonal; public, private, and intimate; formal and informal—around the issue of smoking. Society in the United States labored into consciousness and, often divided against itself, increasingly rejected smoking as an acceptable behavior.

AIDS Prevention

The communication process that is emerging around AIDS prevention is similar in many respects. Will individuals change their behavior in time? Will society shift its mores and support systems to respond adequately to a new world with

AIDS? It should be noted that the world cannot afford the two decades that the change in adult smoking behavior in the United States required.

The WHO Special Programme on AIDS believes that improved health promotion methods combined with the acceleration of processes illustrated by the reduction of cigarette smoking in the United States point to the possibility of success for AIDS health promotion programs. Initial positive changes in knowledge and sometimes practices for targeted populations are being reported in the United States, Britain, Australia, Sweden, Switzerland and Kenya.[4-7] Major controlled intervention forces under the leadership of the World Health Organization, including governmental and private health systems, nongovernmental organizations, educational systems, and hundreds of smaller, targeted interventions at the community level are combining with widespread coverage in the popular media.

Conclusion

The challenge to health promotion presented by AIDS prevention is to enter into both programmatic and societywide communication processes as a catalyst to accelerate their interaction, their efficacy for positive change and their ultimate impact. Insofar as health promotion can succeed in this agenda, it can contribute significantly to changing the global face of AIDS.

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AIDS Prevention and Control in Japan

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Surveillance for the acquired immunodeficiency syndrome (AIDS) in Japan started in September 1984 and in February 1987 was extended to seropositive carriers of human immunodeficiency virus (HIV) antibodies. A total of 2,000 hospitals and clinics throughout the country have actively participated in the surveillance. An educational program for health care workers, including physicians, was initiated in July 1985 by issuing a series of government memoranda and distributing pamphlets and posters. Counseling programs for people concerned about AIDS and laboratory support to provide screening services have been developed. Laboratories that can also perform confirmatory tests will be established shortly. The screening of all donated blood was established in November 1986.

Education programs for the public have been conducted mainly through the production and distribution of various materials and pamphlets. Research has been focused primarily on diagnosis and treatment, with international cooperation emphasized. A new act of legislation has been proposed in the Parliament that will require mandatory reporting of cases of AIDS and HIV infection with confidentiality preserved. Further debate may be needed to reach national consensus on this issue. The proposed law will not include provisions that would affect international travelers, foreign students or immigrants.

(Tamashiro H, Kawaguchi Y, Ito M: AIDS prevention and control in Japan, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:719-722)

The first case of the acquired immunodeficiency syndrome (AIDS) was reported in Japan in March 1985, and as of August of this year, 50 cases have been reported to the Ministry of Health and Welfare. Although the number of AIDS cases is increasing in Japan, the prevalence rate is much smaller than that of countries in North America and Western Europe.

A surveillance system was established in September 1984 to identify cases of AIDS as soon as possible and to prevent secondary infection. Laboratory screening for the human immunodeficiency virus (HIV) antibody in donated blood was initiated in two large metropolitan cities (Tokyo and Osaka) in February 1986 and was expanded nationwide in November 1986. As of August 1987, 298 HIV-antibody carriers have been reported throughout the country.

Epidemiology

Of the 50 reported AIDS cases in Japan, 46 are male and 4 are female; 28 have died (Table 1). A breakdown of the male cases is 29 hemophiliacs, 15 homosexuals (of whom 3 are foreigners), 1 heterosexual and 1 case of undetermined origin. Of the four women, two are foreigners and all are heterosexual. The first Japanese female case, known as the "Kobe case," is a 29-year-old woman who had been married to a foreigner and lived abroad. She divorced her husband, returned to Japan and apparently was a prostitute for six to seven years in the Kobe area, Hyogo Prefecture, before she was diagnosed with AIDS in January 1986.

Following publicity in the Kobe area, approximately 12,000 consultation visits and telephone inquiries to the city authorities were made from all over the country, and more than 4,800 serologic tests were performed for concerned residents within five weeks. The test results indicated no seropositivity among those concerned. This woman's case brought a lot of publicity, which stimulated formation of the national AIDS prevention and control program in Japan, including proposed legislation on AIDS.

Of the 298 people identified as seropositive for HIV, 248 (83%) have hemophilia and 24 (8%) are homosexual, 18 (6%) heterosexual and 8 (3%) undetermined. Of the heterosexuals, 14 are men, and all had contacts with female prostitutes while abroad in Africa, Europe or the United States. Three seropositive women are spouses of infected hemophiliacs. Two others, a man and a woman, are believed to be infected by domestic heterosexual contact. About 50% of all carriers so far reported are within the 20- to 48-year age groups (Table 2).

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Surveillance

Surveillance of AIDS cases began in September 1984 in collaboration with approximately 600 hospitals and clinics throughout the country after the establishment of a National Committee on Survey for AIDS. In May 1986 the number of the collaborating institutions was expanded to approximately 2,000. A Subcommittee on AIDS Surveillance was organized under the newly renamed National Expert Committee on AIDS.

The surveillance system for seropositive persons, separate from that of AIDS cases, was also established in February 1987. At present the two independent systems are in operation under the AIDS Surveillance Committee.

Both surveillance systems are voluntary reporting systems based on a network of the approximately 2,000 collaborating institutions all over Japan. They consist primarily of all national hospitals, other public general hospitals and those institutions, including health centers and clinics for sexually transmitted diseases, that the prefectural governments specifically request for collaboration.

The current surveillance systems on AIDS, suspected cases as well as HIV-seropositive persons, are shown in Figures 1 and 2. The Ministry of Health and Welfare requests the collaborating hospitals and clinics, through the 47 prefectural governments, to report cases and suspected cases of AIDS using a structured questionnaire originally prepared by the National AIDS Experts Committee. The report form includes the name of the collaborating institution and the following information about the patient:

- social and risk factors, including past and present status of sexual life and treatment history;

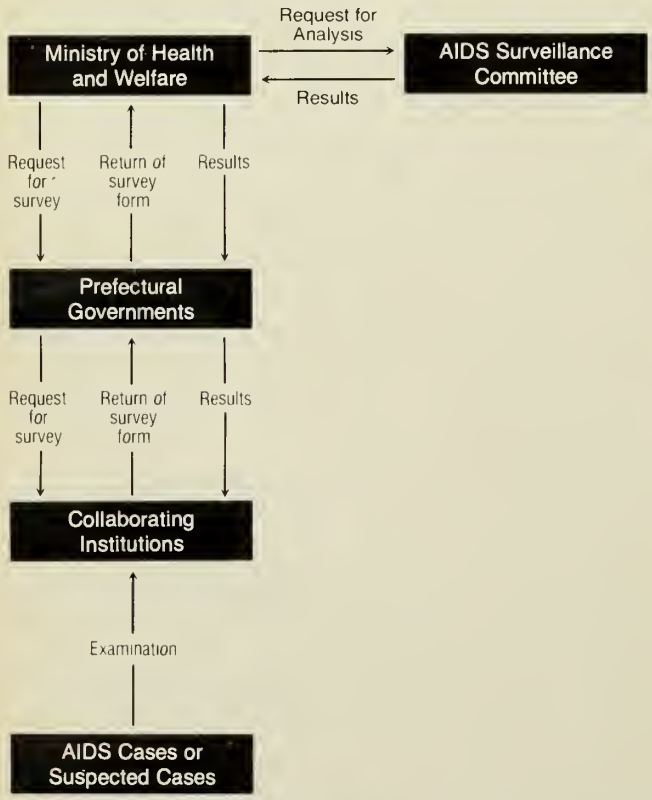

Figure 1.—Nationwide survey system for AIDS cases and suspected cases as of February 1987. Note: Follow-up of reported cases would be made when and if necessary.

TABLE 1.—*Cases of the Acquired Immunodeficiency Syndrome (AIDS) By Sex and Risk Group and Seropositive Carriers, As of August 1987**

Risk Group	AIDS Cases, No. Male	Female	Total	Carriers, No.
Homosexual	15 (4)	...	15 (4) [6]	24
Heterosexual contact	1	4 (2)	5 (2) [3]	18
Hemophiliac	29	0	29 [18]	248
Unknown	1	0	1 [1]	8
Total	46 (4)	4 (2)	50 (6) [28]	298

*( ) denotes foreigners and [ ] deaths.

TABLE 2.—*Carriers of the Human Immunodeficiency Virus (HIV) By Age, As of August 1987*

Age, Years	HIV Carriers, No.
<20	111
20-29	88
30-39	51
40-49	18
≥50	26
Unknown	4
Total	298

- opportunistic infections/AIDS-specific diseases;
- nonspecific diseases;
- signs and symptoms lasting more than one month after onset (suspicion);
- other diseases before onset;
- immunosuppressive treatment for three months before onset;
- laboratory results, including status of HIV antibody;
- consanguineous marriage;
- physician's comments.

The collaborating institution forwards the completed report form to the Ministry through the prefectural government. The Surveillance Committee then analyzes these reports and reports the results to the Ministry. The Ministry then regularly makes public announcements on the results in terms of number of cases and deaths by risk factor. The collaborating institutions would, if necessary, follow up the suspected cases on the basis of the Ministry's report.

The surveillance system for seropositive persons is basically the same as that for AIDS except that the collaborating institutions may send back the survey forms directly (without passing through the prefectural governments and the Ministry) to the Surveillance Committee. This survey form includes information on the reporting institutions, the age and sex of patients, method of transmission, presence or absence of signs and the laboratory methods used for HIV antibody testing.

The Ministry periodically announces the results of monthly and cumulative number of seropositives, which are subject to analysis by the Surveillance Committee. The collaborating institution that reports a positive carrier is not obliged to follow up cases in the present surveillance system. Both report forms are treated strictly confidentially.

Preventing Secondary Infections

The education program for health care workers was initiated in July 1985 by issuing a government memorandum for-

mulated by the Ministry of Health and Welfare on the precautions recommended regarding management of AIDS patients. Along with the expansion of a surveillance network, information on health education for AIDS patients and HIV carriers was distributed to all collaborating institutions for surveillance. This includes information on general preventive measures such as no sexual contact with high-risk groups, no anal intercourse, and the use of condoms; preventive measures in the homes of AIDS patients and in health care facilities; preventive measures for HIV seropositive persons, and confidentiality for patients, healthy carriers and their families.

The Ministry of Health and Welfare also issued a memorandum in 1987 on the prevention of HIV infections to assist the local governments and organizations in carrying out community health education on AIDS. The memorandum contains, among other things, a general description of AIDS, general preventive methods, including prevention of infection from blood or sexual transmission, preventive measures for secondary infection from seropositive persons and a discussion of other subjects, including confidentiality of information obtained.

Consultation Program for the Public

The consultation program for the public on AIDS was encouraged by establishing in 1985 at least one focal consultation clinic for concerned people in all prefectures of the country. This program has been expanded, and such consultation can now be made in at least one clinic in each of the prefectures and at all of the approximately 850 health centers throughout the country. Two national workshops for counselors were held in 1985 and 1987.

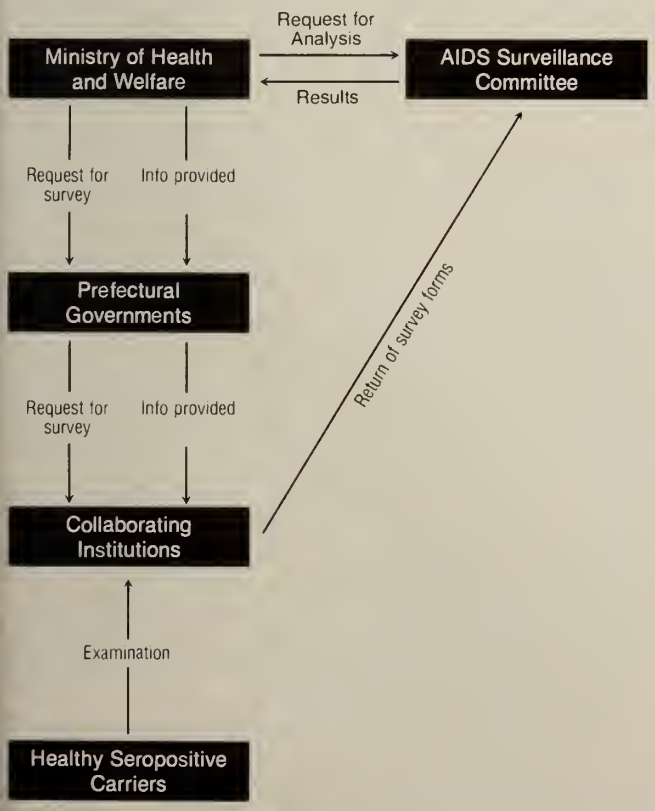

Figure 2.—Nationwide survey system for seropositive persons (carriers) as of February 1987.

Establishment of the Laboratory Systems for Screening

Laboratory support to ensure that at least one laboratory center in each prefecture can provide screening and confirmatory test services has been developed. The screening is based on enzyme-linked immunosorbent assay or particle agglutination testing, with the diagnosis confirmed with either indirect immunofluorescence assay or the Western blot test. The National Institute of Health in Tokyo and 16 prefectural public health laboratories have been equipped and personnel trained for the supplementary testing by immunofluorescence methods for confirmation. According to the national plan, however, at least one laboratory center in each prefecture that can perform both screening and supplementary confirmation tests will be established by September 1987.

Program on the Safety of Blood and Blood Products

In Japan the majority of patients with AIDS are hemophiliacs who were treated with imported factor VIII and IX concentrates from the United States. Because the HIV antibody is found among patients with hemophilia, the treatment procedures for those factors would be extremely important in Japan. The high prevalence of HIV infection in patients with hemophilia A and hemophilia B has led the government to introduce safer factor VIII and factor IX concentrates with heat treatment. These were approved by the government in July and December 1985, respectively.

In addition to heat treatment of blood products, HIV antibody testing on the original blood materials has been introduced. Screening tests on donated blood for HIV antibodies were started in February 1986 in Tokyo and Osaka with nationwide expansion intended. In July 1986 the screening program was widened to include eight prefectures. The nationwide screening on all donated blood was then established in November 1986. Approximately 9 million units have been tested each year for HIV antibodies.

It is thought that the risk of HIV infection by blood and blood products is at least greatly reduced and probably eliminated through these preventive measures.

Public Education Program

Education programs for the public have been conducted mainly through the production and distribution by the government of various materials and pamphlets, in collaboration with the National AIDS Experts Committee:

- October 1985—a leaflet for public distribution on "AIDS: Acquired Immunodeficiency Syndrome"
- February 1986—a textbook, *AIDS in Japan*, for teaching personnel
- February 1987—a pamphlet on "What is AIDS?"
- March 1987—a revision of the *AIDS in Japan* textbook
- March 1987—"AIDS" (translation of the United States Surgeon General's report and detailed information for teaching personnel)
- March 1987—A guideline for the medical care of AIDS patients for physicians and production of a poster and videotape.

Research

Research projects are underway at the National Institutes of Health, universities and other Japanese institutions. Re-

search priorities during the past several years have been focused mainly on diagnosis and treatment. Research projects include, among other things, studies on the safety of blood and blood products, improvement of the indirect immunofluorescence assay, development of an immunoadhesive hemagglutination assay, mechanism of the pathogenesis of AIDS, prevention and treatment of HIV carriers and the development of a qualitative assay method for HIV.

To facilitate, promote and coordinate research on AIDS, as well as to advise the Ministry on the prevention and control on the basis of that research, an Advisory Committee on AIDS Control was established by the Ministry of Health and Welfare. The committee consists of 19 experts from the fields of medicine, microbiology, epidemiology, immunology, hematology, pathology, pediatrics, dental surgery and medical zoology. The cabinet also has formulated a coordination meeting on AIDS Prevention and Control, consisting of 14 ministers headed by the Minister of Health and Welfare. The government plans to strengthen exchange of information with foreign countries and international organizations and to contribute to the prevention and control of the spread of AIDS worldwide.

Legislation

A new law concerned with the prevention of AIDS was proposed in the Parliament in early 1987, with a view to determining the necessary measures for preventing the spread of AIDS, as well as to contribute to the improvement and advancement of public health. The proposed law consists of 16 articles, including specification of duties of the prefectural and local authorities, the public and physicians, reporting of seropositive persons (carriers), confidentiality and punitive provisions.

In the proposed law, a person found to be infected with HIV must be notified by a physician and reported to the local authorities. The prefectural governor can not only recommend that a person suspected of having HIV infection have a medical examination but can also order punishment of that person if the recommendations are not followed.

At present, there is no requirement for HIV screening of international travelers in Japan, including foreign students or immigrants. The proposed law will not include any provision that would affect these groups. There is currently a move, however, to add AIDS to the list of infectious diseases that are exclusionary conditions under the existing law in Japan.

Emerging Patterns of HIV Infection and Control in the Philippines

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A total of 50 carriers of the human immunodeficiency virus (HIV), 46 of them female prostitutes, have been detected through seroprevalence surveys by the Department of Health, Manila. Infection rates are highest in two small cities near foreign military bases and in the tourist district of MetroManila. Nine patients with the acquired immunodeficiency syndrome (AIDS) who contracted the disease outside the country have been reported, with opportunistic infections being the major clinical feature. Public information measures heavily utilize the mass media, and there is anecdotal evidence that awareness of the disease among the urban population is increasing. The National AIDS Committee foresees that a large proportion of the cases seen in the Philippines over the next few years will be returning nationals who were infected abroad.

(Dayrit MM, Monzon OT, Basaca-Sevilla V, et al: Emerging patterns of HIV infection and control in the Philippines, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:723-725)

As of July 31, 1987, a total of 46 female prostitutes have been found seropositive for the human immunodeficiency virus (HIV) antibodies. There have been 53,376 tests done among these women working in bars and nightclubs all over the country. All except two were found in the cities of Olongapo, Angeles and MetroManila. The others were found in La Union (northern Philippines) and Iloilo (southern Philippines) (Figure 1). Repeated positive tests by enzyme-linked immunosorbent assay were confirmed by the Western blot test.

Of the 46 infected prostitutes, 40 (87%) were found in the Angeles City and Olongapo areas that are adjacent to foreign military bases. The 40 carriers were detected from among 34,998 blood examinations, for an overall HIV antibody positivity rate of 1.1 per 1,000. These examinations were done over a 26-month period and represent an accumulation of tests done on different women, as well as serial tests done on the same women at a minimum interval of six months. The first infection was detected in May 1985.

There are approximately 10,000 registered "hospitality girls" (a euphemism for prostitute) in Angeles and Olongapo at any one time; however, a substantial proportion of this population frequently changes addresses. The above estimate comprises about half the total registered throughout the country. The total number of unregistered "girls" is undetermined and could be two to three times the number registered.

Longitudinal studies in Angeles showed a low seroconversion rate of only 1.4 per 1,000 among seronegative prostitutes followed up for the first 12 months. Two infected prostitutes are currently pregnant; another two carriers had their pregnancies aborted. In general, there has been no progression of the disease among asymptomatic carriers, but it is too early to predict their eventual clinical outcome.

In the MetroManila area, four prostitutes have been found positive from among 10,549 tested, yielding an antibody positivity rate of 0.4 per 1,000. Three of the four carriers work in clubs located in the Ermita district, which tourists frequent. The antibody positivity rate for Ermita is 1.1 per 1,000.

Tests have also been conducted by the Department of Health among 867 male homosexuals, and only one individual—from Olongapo—has been found seropositive. To date only three other infections have been reported by private sources, and two of these are in male homosexuals. No infection has been detected in 3,200 blood donors or in 12,000 overseas workers. No seroprevalence surveys have been conducted among merchant seamen who, because their cargo ships dock in African ports like Mombassa, are also at risk for HIV infection.

There have been nine cases of the acquired immunodeficiency syndrome (AIDS) reported, all occurring in persons who contracted the disease abroad. Seven were Filipinos: four homosexual/bisexual men, one elderly woman whose

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TABLE 1.—*Clinical Manifestations in Nine cases of the Acquired Immunodeficiency Syndrome in the Philippines*

Opportunistic Infection	*No of Cases*
Candidiasis	3
Post *Pneumocystis carinii* pneumonia	3
Mycobacterium avium-intracellulare	2
Cryptosporidiosis	2
Toxoplasmosis	2
Pulmonary tuberculosis	1
Herpes zoster	1
Cryptococcosis	1

infection was traced to a blood transfusion and two persons whose personal data have been kept confidential by their private physician. All cases manifested with opportunistic infections (Table 1); no opportunistic tumors were diagnosed.

The identities of the nine AIDS patients have been kept confidential, and information about their clinical condition has been acquired with great discretion. All patients have died or have left the country. These early trends suggest that returning Filipino nationals will comprise the bulk of AIDS cases in the Philippines within the next few years.

Projected Incidence of Infection

Judging from the current levels of infection, the National AIDS Prevention and Control Committee of the Department of Health considers the Philippines to be at an early stage of the AIDS epidemic. This means that the virus is already infecting segments of the population, although indigenous AIDS cases have not appeared. The committee recognizes that the exponential rise in cases currently observed in other countries is a consequence of the steady accumulation of infected persons during the late 1970s and early 1980s when the virus spread unnoticed. The committee is pushing for measures aimed at minimizing the spread of the HIV infection and assisting those already infected.

Figure 1.—This map shows the geographic distribution of human immunodeficiency virus-seropositive prostitutes in the Philippines.

What follows is the Philippines' AIDS control plans during the period from July 1987 to December 1990. The present data on infection rates among prostitutes are used as the basis for projections.

If we assume that the current rates of infection are actually ten times more than available measurements—and judging from the experience of other countries, this is not an unreasonable assumption—there might be roughly 500 cases of HIV infection in the country today. If 30% of these cases progressed to AIDS within the next five years, we would be seeing about 150 cases of AIDS in the Philippines by 1992, not including imported cases.

If we further assume that infections double every year until 1990, we may expect 4,000 total cases of HIV infection by 1990. These could result in approximately 1,000 cases of AIDS by 1995. All these figures are speculative and are given for purposes of planning. The AIDS Committee projects that the country will be seeing 300 cases by 1990, many of which will most probably be imported.

Strategy of a National AIDS Control Program

The strategy of AIDS control in the Philippines is to block the three main routes by which the virus spreads: sexual activity, contaminated blood supply and from infected mother to child. Initial evidence suggests that the main route of spread is heterosexual. The Philippines does not have a problem with intravenous drug abusers.

Coupled with its effort to disseminate information through the mass media, the Department of Health is initiating and encouraging programs for the counseling and care of asymptomatic carriers and patients with the disease. Already, licenses of infected prostitutes are being revoked, and these women are being persuaded to change their occupations. To succeed, control measures need the cooperation of individuals and organizations in both public and private sectors.

The main areas of concern for the implementation of control activities are: surveillance and laboratory testing, education, personnel development (counseling, clinical management, research) and organization of local AIDS committees in Angeles, Olongapo and Manila.

Surveillance

During the next three years, surveillance activities will focus on the following:

- High-risk behavior groups. These include persons involved in occupations that trade sex for money—female and male prostitutes, homosexual and bisexual men and attendants of massage parlors and sauna baths. These groups can be followed up as sentinel populations because requirements for licensing and work permits now provide for HIV screening, along with testing for syphilis and gonorrhea. Overseas workers (entertainers, merchant marines, laborers) may, in the course of their job applications, also require testing. Because most of them have tests performed in private laboratories, reports from these laboratories will provide a clue to the level of infection in these groups. Cohort studies among volunteer homosexual men are also proposed.

• Commercial blood donors. Infection has yet to be detected among commercial blood donors, but as part of the program to prevent transmission of pathogens through this route, the Department of Health recommends mandatory screening of commercial blood donors. The committee supports the policy of voluntary blood donation over the long term. Screening of volunteer donors can be done through history, physical examination and self-exclusion.

Education

Health education programs will be designed to discourage high-risk behavior among specific occupational groups (prostitutes, for example) and the general population. The committee envisions that the approach to different segments of the population may need to vary to be effective. For example, explicit messages like "use condoms" may be appropriate for posters in bars and massage parlors but inappropriate for general consumption. Messages for the general population could dwell on information about routes of infection while avoiding prescriptive advice on condom use. A message like "AIDS does not discriminate . . . you can" is deemed more culturally acceptable on television. Educational materials will need to be developed and appropriately field tested. Health education programs for overseas workers are being undertaken in cooperation with the government's Philippine Overseas Employment Administration.

Personnel Development

The Department of Health is developing training programs for counselors, laboratory technicians, clinicians and researchers who can competently deal with HIV infection and AIDS. The type of training will necessarily differ depending on the level of expertise to be acquired. The staff of sexually transmitted disease clinics and regional laboratories will need to acquire the competence to do HIV screening and counseling as soon as possible. Training of researchers on retrovirology and immunology will be crucial over the long term, and committed persons who can qualify for training will be identified.

Local AIDS Committees

The Department of Health has issued directives to set up local committees that will oversee efforts to control AIDS and sexually transmitted diseases in the cities of Angeles, Olongapo and Manila. The mayors of Olongapo and Angeles have already issued executive orders mandating the creation of such committees. These committees will be chaired by the city health officer and should include members of the other government agencies—social welfare and local governments. These committees will work closely with the sexually transmitted disease clinics, which are under the supervision of city health officers. One of their main responsibilities is to create programs that could provide infected hospitality girls with alternative occupations after their licenses have been revoked.

Role of Media

Mass media have played a major role in disseminating information about HIV infection and AIDS. The Department of Health has regularly briefed reporters on the technical aspects of the disease to ensure that accurate information is reported to the public. Thus far, newspaper articles and radio and television broadcasts have been the major ways to inform people about the problem at a time when monies to fund the production and distribution of print materials (leaflets, posters, brochures) are still being sought.

One recent television show featured interviews with infected prostitutes whose true identities were not revealed. Another popular television soap opera dramatized the psychosocial dynamics in the lives of a prostitute, a young businessman whom she infected and the businessman's wife. Spontaneous public feedback underscored the effectiveness of broadcast drama in delivering health messages to the public. The number of consultations in sexually transmitted disease clinics in Manila more than doubled the week immediately after this show was aired.

Conclusion

In a country where pneumonia and diarrhea still claim an estimated 400 lives of children daily (unpublished data, Department of Health, 1986), where more than 350,000 persons are estimated to be sputum positive for tuberculosis (unpublished data, National Institute for Tuberculosis, 1984), and where 2 in every 100 persons in endemic areas harbor malaria parasites (unpublished data, Department of Health, 1986), the AIDS problem is relatively small. However, apart from the devastation of AIDS per se, morbidity and mortality patterns from other diseases, notably tuberculosis, could worsen if the virus spreads unchecked. There is really no time to lose in getting organized efforts underway so that individuals and communities are accurately informed and properly persuaded to protect themselves against the HIV infection.

Towards a National AIDS-Control Program in Uganda

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A national AIDS-control program was developed in Uganda to deal with a potentially serious epidemic of the acquired immunodeficiency syndrome (AIDS). A cumulative total of 1,138 cases of AIDS has been reported in Uganda between 1983—since AIDS was introduced into the country—and March 1987. More than 80% of the victims are sexually active persons whereas less than 10% are infants and children younger than 5 years. Virtually no cases or seropositivity is reported in persons between the ages of 5 and 14 years or after the age of 60 years. Most transmission has been through the heterosexual route, and, unlike in the United States, the male-female ratio is 1:1. Heterosexual high-risk behavior is cited as an important mode of transmission. A survey of household contacts showed that despite the closeness, only the sexual partners were seropositive.

A five-year plan of action has been developed, and health education is the main thrust. It also includes blood screening, improved sterile procedures, improved surveillance and notification, research and terminal patient care. The plan stresses integration based on primary health care. There are unresolved moral issues of whether or not to tell the truth to an AIDS victim or any healthy seropositive person in developing countries, especially unstable persons. The best approach is to sensitize everyone so that they become guardians of their lives because sexual behavior is an issue of individual responsibility.

(Okware SI: Towards a national AIDS-control program in Uganda, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:726-729)

The acquired immunodeficiency syndrome (AIDS) could turn out to be the greatest medical challenge of this century. This worldwide pandemic is presenting more unique problems than we can ably cope with. AIDS has spread to several African countries,[1-3] especially those of Central and East Africa, which appear to be most affected. At present inadequate infrastructures make it difficult to meet the increasing demand for relatively specialized services to respond effectively to the epidemic.

Uganda is one of those affected. Situated in the heart of Africa along the Equator, Uganda is a focal point of human interaction and trade routes. It is on a high plateau, evergreen and warm. More than 90% of the estimated 15 million population live in rural areas while less than 10% live in urban areas. The southern part of the country is fairly densely populated, especially along the townships of the Trans-African Highway to the Indian Ocean ports (Figure 1).

The First Cases

The first cases of AIDS in Uganda were suspected during the last quarter of 1982 when several businessmen died at Kasensero, an isolated small fishing village on Lake Victoria. This small town was also known for smuggling and illicit trade, and when these deaths occurred fellow traders shrugged it off as witchcraft. Others thought it was natural justice against those who had cheated. The only common characteristic the victims had was that they were all young and sexually active and stayed away from home for several days chasing wealth and presumably using it generously for their recreation and merriment. Soon there were corresponding deaths among the spouses. The social victimization and prejudice that followed led to migration to bigger towns inland, to the capital and to places beyond, which hitherto had not experienced the disease.

It became clear that we were dealing with a completely new disease. In the subsequent years, the number of cases increased from 17 in 1983 to more than 1,000 by 1987 (Table 1).

Epidemiology

The reasons for the rapid increase in the number of cases may be attributed to an open and frank government policy as well as to active surveillance.

The age distribution of the cases has remained constant—that is, it appears to be a disease of the young, sexually active groups. Nearly 70% of the victims were between the ages of 20 and 40 years. It was striking that there were virtually no cases in persons between the ages of 5 and 14 years nor among the elderly. The latest returns show an increasing number of

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
NCPA = National Committee for the Prevention of AIDS
WHO = World Health Organization

infants and children younger than 5 years (Table 2), which could suggest the ever-increasing role of vertical transmission.

Surveys carried out suggest that heterosexual contact was probably the most important mode of transmission. Unlike in the United States and Europe, homosexuality is virtually nonexistent in Uganda—or Africa, for that matter. Our surveys suggest that having multiple partners, as in prostitution, is a high-risk behavior. On the other hand, school children aged 5 to 14 years and the elderly (over 60 years) were associated with a very low risk indeed (Table 3). Virtually none of the school children nor the elderly showed evidence of infection with the human immunodeficiency virus (HIV).

AIDS in Uganda is a disease of urban areas. The incidence among antenatal mothers is 13% in Kampala and may usually be associated with a sexually transmitted disease complaint. The incidence in remote traditional districts such as West Nile and Tororo districts is virtually zero (1987). There is a clear difference between urban areas, where sex is liberal, and rural areas where there are stricter codes of morality.

Mosquitoes and other vectors have also been considered. The local people believe that mosquitoes could be as responsible as the use of needles and syringes. This is unlikely, however. A recent household survey of 114 household contacts of 25 AIDS victims showed that only the sexual partners were infected, while the rest of the household casual contacts such as children, adults and other relatives were free from infection.

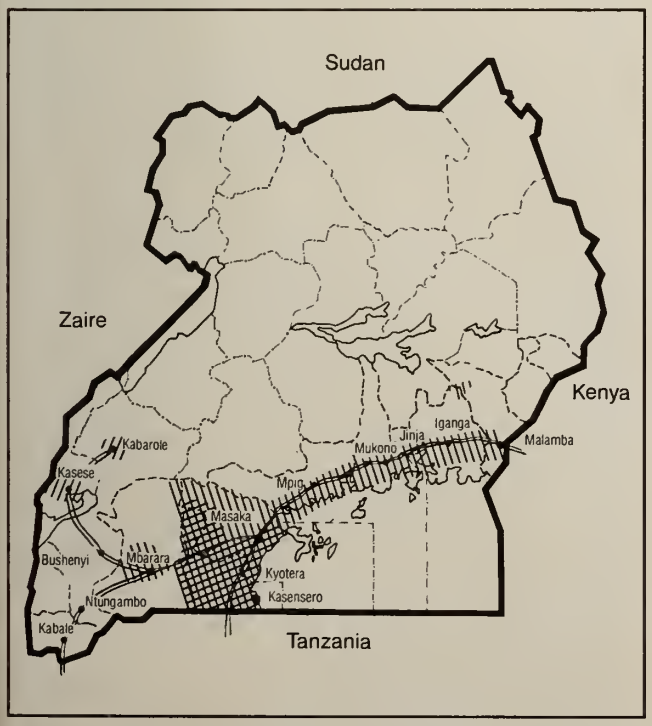

Figure 1.—The map of Uganda shows infected areas (1987). ▨ = newly infected areas and districts (1987), ▒ = endemic areas (1985), ⟷ = international trade routes and stopping towns

Since the disease first appeared in 1982, it has spread fast. The disease is spreading eastward along the Trans-African Highway, which handles considerable human traffic and interaction; 33% of long-distance truck drivers are infected. Civil disturbance that leads to the displacement of large adult populations is also a factor to be considered in the further spread of the disease.

Social Consequences of Infection

To tackle the AIDS problem, the medical and social consequences of HIV infection should be taken into account. For example, some medical conditions of significant public health importance are on the increase. We are experiencing epidemics of tuberculosis and other diseases, and the infant mortality rate will continue to rise as a result of vertical transmission from infected mothers to their newborns.

The social consequences are even more somber. Death at the most productive age is frustrating and painful to the family, the community and, indeed, the government. In Africa and Uganda, for that matter, death is an important event during which no other socioeconomic activity can be undertaken. AIDS deaths on a large scale could mean fewer harvests, with the inevitable famines in many rural areas giving way to the vicious cycle of poverty, ignorance, disease and death. We have also got to address ourselves to the basic moral issues of whether or not HIV-infected persons should be allowed to marry and procreate. These issues stretch anyone's imagination, especially in African societies where traditional values are associated with children and inheritance.

TABLE 1.—*Number of New Cases in Uganda (Cumulative), 1983-1987*

Year	*New Cases (cumulative), No.*
1983	17
1984	29
1985 and 1986	910
1987 (through March)	1,138

TABLE 2.—*Age Distribution of Cases in Uganda, 1987*

Age, Years	*New Cases, No.*	*Percentage*
0- 4	14	10
5-14	1	1
15-19	10	7
20-39	96	69
40-59	18	13
60+	0	0
Totals	139	100

TABLE 3.—*Comparison of Seropositivity Rates Among High-Risk Groups and Low-Risk Groups, Uganda (1986)*

Risk Groups	*Sample, No.*	*Seropositivity, %*
High-risk group		
Prostitutes, bartenders (Rakai)	186	86
Long-distance truck drivers (Lyantonde)	74	33
Low-risk group		
School children aged 5-14 years (Kasese)	200	0
Elderly aged 60+ years (Kampala)	74	0

Strategy for Control

A comprehensive AIDS-control program must take several factors into consideration.

- First, it must be recognized that AIDS is not just a medical problem, but has social and spiritual dimensions.
- Second, all efforts against the disease must be integrated into the existing health care system. The strategy must have multidisciplinary and multisectorial components. AIDS control must be integrated in the overall primary health care strategy in the health care system and must make use of all available resources at the community level, our primary frontline against the spread of the disease.
- Third, it must be recognized that AIDS is a new disease with new demands—especially financial—that must explicitly be made available.
- Fourth, the need for speed and a minimum of bureaucratic red tape is vital. AIDS is a sensitive disease and, before any program can take off, there must be political commitment at the very top to guarantee open and frank discussion about the disease. There is no vaccine or drug against it as yet. For this reason, we have decided to maintain a policy of openness and frankness about the disease because the only way at the moment to prevent AIDS is by health education.

Limited financial resources mean that we have had to tackle those activities for which the least financial outlay produces the most benefits in the shortest possible time.

Organizational Framework

A decision was quickly made to form a National Committee for the Prevention of AIDS (NCPA) that is multidisciplinary, multisectorial and extensively broad-based. The committee comprises physicians, academics from the University of Uganda, educators, administrators, security forces, the political movement, church leaders and nongovernmental agencies and representatives from other ministries coordinating social services. The NCPA role is advisory and formulates primary policy. It was generally agreed that the Ministry of Health would maintain a leadership role in all technical matters. A coordinating implementing unit called the AIDS Control Program was established directly under the Minister's office. This was to ensure that the AIDS Control Program does not divert resources from the regular medical activities, which are equally important, and that there is no unnecessary competition for the limited AIDS funds. Bureaucratic procedures would be cut to a minimum. There was no need to strengthen coordination at the district and subsequent lower levels to ensure that there was total integration of the AIDS Control Program with primary health care. The fact that there are team leaders at each of these levels ensures accountability and responsibility and facilitates the flow of information from the top to the grassroot levels.

This infrastructure is the basis for an emergency six-month program, to be followed by a long-term five-year program.

The Main Activities

Generally speaking, measures against AIDS will entail improving measures to prevent other infections. The health infrastructure must therefore be improved to keep infections and AIDS at bay. The following listed items will be our priority concern, with health education being our main thrust:

- Health education.
- Screening of blood and improvement of blood transfusion services.
- Improved sterile techniques.
- Improved surveillance, through notifications and surveys.
- Research—seroepidemiology and social research.
- Improved patient care.

Health Education

Health education is the main thrust of the AIDS Control Program. It entails making use of all facilities to disseminate health information and education. We have recognized that the town and urban dwellers are a special risk group in the most danger. Messages have been put on local television and radio programs urging people to "love carefully" and to avoid indiscriminate sexual relations. Unfortunately, television, radio and newspapers are not available in rural areas where most of the people live. Illiteracy and relative ignorance are a part of life for most people in the rural areas. Fortunately, at least for the time being, there are strict codes of morality that forbid casual sexual relations in the rural areas. The program has also focused special attention on some potentially high-risk groups such as schools and workers in places of entertainment.

To educate the rural people, we have made use of the political structure at the grassroots level. His Excellency the President has incorporated health education in speeches at most of his rallies, which are usually well attended. "Resistance committees" are responsible for household contacts. They have received elementary but effective reorientation about AIDS, which information they eventually pass along from door to door. The Catholic, Protestant and Moslem churches are deeply rooted in the villages, and the clergy, like the schoolteachers, has preached "the gospel according to AIDS," asking their flocks to change their ways by "loving faithfully" and maintaining "zero grazing"—an agricultural metaphor for having only one sexual partner at a time. For many people, it is sometimes hard to assimilate the bitter facts about AIDS transmission. We need to soften our campaign with light jokes and comic plays by theater groups.

Blood Screening

It would be gross malpractice to transfuse anyone with contaminated blood. The provisional high rates of infection of donated blood mean that between 5% and 15% of those transfused could become infected. Instituting blood screening has been handled as an absolute emergency. In 1986 we had only limited screening facilities in Kampala, but by May 1987 there were at least 13 readers of enzyme-linked immunosorbent assays (ELISAs) in centers in all the regions, especially in the HIV-endemic areas and along the corridors of the trans-African route. Another sector that is receiving considerable attention is the National Blood Transfusion Service, which is being improved and rehabilitated to cope with the AIDS epidemic.

Improved Sterile Procedures

To protect the public and health workers, several orientation courses in sterile techniques have been mounted. This has been accompanied by improvement in actual facilities. More sterilizers for the rural areas were acquired for health centers and hospitals. Needles, syringes and disinfectants were pur-

chased in substantial quantities. An additional quantity of gloves, aprons and surgical boots was a must, especially for midwives and traditional birth attendants. The gap between demand and supply remains wide, however.

Improved Surveillance

When the program started, the exact number of cases was not known. There was overdiagnosis, misdiagnosis and sometimes underdiagnosis of cases. Notifications were minimal. First, we had to ensure that the World Health Organization (WHO) case definition for AIDS was reliable in our situation. Fortunately for the WHO criteria, sensitivity, specificity and the predictive values were high. Hospital-based data collections were streamlined, and a task force of epidemiologists carried out several baseline surveys on the countrywide extent of the disease. This will be followed by longitudinal surveys at six-monthly or yearly intervals.

Research

More epidemiologic research is important to identify local risk factors associated with transmission. Research will certainly help improve surveillance. Our current priority is on understanding factors—especially social—associated with transmission. Several sociologic studies on knowledge, attitudes and practices are being undertaken, and more are planned; the main purpose is to understand the cultural practices before the condom can be fully promoted. Before that can be ascertained, we have to be cautious when advocating condom use. Basic virologic research has also been strengthened by establishing new quality control facilities at the Uganda Virus Institute, which we hope will become a regional AIDS collaborating center.

Clinical trials of local herbs to treat the AIDS victims have received considerable support from both the medical and general populations. Several studies are going on, but it is too early to be optimistic.

Patient Care

Admittedly, there is little that can be done for the patients, but they need palliative terminal care and, indeed, general maintenance. There are psychological and spiritual needs to be reckoned with, and the community fortunately has assumed full responsibility in the traditional way. The churches have taken up some of this load by counseling and delivering spiritual management. The idea of a hospital ward for these patients is being contemplated, but such an institution could be like a prison ward with condemned inmates. In any case, what extra good can be done? Will patients agree to stay, especially when there is so much stigma about the disease? Will enough health and nursing staff volunteer for this task? Perhaps for the moment, the traditional community system should be helped to take care of these patients within the communities, and small grants could be given to individual families.

Funding

We must make reference to budgets and funding of the AIDS Control Program. AIDS control is a costly enterprise. One screening test costs about US $1. A confirmatory Western blot method is around US $0.65 per test, and viral isolation is even more expensive. A complete ELISA reader center is close to US $10,000. Yet, the average per capita expenditure on health in many African and developing countries is around US $1.70. This is the dilemma.

AIDS is a new disease that has created new financial and material demands. The World Health Organization should assume the leadership in mobilizing and coordinating both technical and financial resources for the disease. WHO should mobilize resources urgently. At a meeting of international interested participating parties in Kampala in May 1987, organized by WHO, adequate funds were raised for the most essential activities for the program. But the gap between needs and resources remains wide. Local donors are being solicited to raise voluntary funds for the welfare of patients and orphans to reduce the traditional burden of these dependents on society. Despite this financial goodwill, AIDS will continue to pose a direct strain on the financial resources of the Health Ministry and the government.

The Unresolved Issues

Several controversial issues remain unresolved. For instance, what does one do in the case of seropositive but healthy persons? What does one tell them? On the one hand, if we are frank, they may commit suicide, and what happens to the dependents? Second, they may not behave responsibly. Some may commit serious crimes or obtain large loans, expecting to default by death. Yet, a good number could survive a little longer even as carriers, and there is always a small possibility of false-positivity.

Third, we have encountered a serious reaction when trying to be frank; AIDS victims do not want to die alone, and they use all their resources and money to spread the disease to as many people as possible. Yet, if we keep quiet about the seropositive results but sensitize everyone fully, the response towards the community may be better because each person usually believes he or she is not yet infected and will try to protect against becoming infected. On the other hand, it may be necessary to inform some, but only for counseling purposes.

There are other serious controversies. Should HIV-positive couples be allowed to marry? Should HIV-infected expectant mothers be allowed to go to full term with their babies? These are some of the sensitive moral issues of public health concern for which we depend on individual goodwill for compliance, cooperation and responsibility. Already the society is overreacting, and there are examples of social prejudice towards the AIDS victims based on unscientific principles. Perhaps in the long run the churches may give us the solutions. For it is important to maintain that while there are some risk groups in AIDS cases, the key in the transmission is high-risk behavior. The best solution at the moment is to sensitize everyone by health education so that they become guardians of their own lives.

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The French National Program for the Prevention and Control of AIDS

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The French policy concerning the fight against the acquired immunodeficiency syndrome (AIDS) is a complete and well-balanced one, using information not only for the general awareness of the general population, but also with the help of specific actions aimed at high risk groups. Screening is mandatory for blood, organ and cell donors, but it must absolutely respect individual rights and the rules of ethics. Therefore it must be voluntary and totally respect privacy and professional confidence. France does not undertake screening at the border, but does inform people traveling to and from the country. The monitoring and medical care will be given daily for ambulatory patients, and in specific hospital services according to the symptoms of the others. To save money and to be more efficient, tests will be grouped in specific laboratories. Research is, with prevention, the only hope of stopping the spread of AIDS. More than 50 laboratories are at this moment working, and important funds and materials have been allocated. International cooperation is needed, along with the coordination of the World Health Organization, and the action undertaken by the European Community, to establish the most efficient methods of preventing the spread of this new viral infection that now concerns the whole world.

(Pompidou A: The French national program for the prevention and control of AIDS, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:730-731)

The objective of the policy on the acquired immunodeficiency syndrome (AIDS) in France is to develop a general, well-balanced approach to the problems surrounding the human immunodeficiency virus infection.

To monitor the treatment of seropositive patients and to organize research efforts, as well as to avoid alarming the general public, the Health and Family Minister created an administrative structure charged with carrying out the different measures adopted by the French Ministry. A national committee was organized, as well, to advise on the sociocultural problems raised by AIDS.

The policy for the prevention and control of AIDS in France is based on five points:

- Prevention through information, statutory standards and screening;
- Training;
- Monitoring and treatment;
- Research, and
- International cooperation.

What follows is a discussion of each of these methods of prevention and control.

Prevention

Information

The national education campaign in France began in April 1987 with a series of measures, including television commercials emphasizing personal responsibility in avoiding AIDS and a nonhysterical approach to the disease —"AIDS is not an epidemic but an avoidable disease." A data base was established by the French Committee for Education and Health and the Doctor's Daily, accessible through a telephone network. An information booklet for health care professionals was written by two groups, one involved in patient care and one with specialized medical training. A brochure for the general public was also prepared by a group of experts. Finally, a billboard campaign and radio commercials were used to support these efforts.

In addition to this program, financed by the Health Ministry and directed by the French Committee for Education and Health, there are many private campaigns against AIDS. At the moment, there are 28 different associations dealing with AIDS.

Statutory Standards

The French government has not yet wanted to adopt legal measures concerning AIDS. Instead, measures of a statutory nature have been taken to limit the spread of the epidemic. The following are the most recent:

- Legalizing advertising for prophylactics—within the scope of the national campaign against sexually transmitted diseases. The advertisements are under the control of a visa commission, itself under the authority of the Health Minister. This commission checks the quality of the commercial and

From the Faculte de Médecine Cochin and the Ministry of Health, Paris.
Reprint requests to Jonathan M. Mann, MD, MPH, Special Programme on AIDS, World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland.
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decides whether the product corresponds to the defined regulations.

• Legalizing the sale of syringes. During an experimental year, syringes may be purchased anonymously in drugstores without a prescription. This measure overrules a 1972 decree that allowed the sale of syringes only with a medical prescription.

Screening

Mandatory, systematic screening is not conducted in France because of the high cost—estimated at 16 billion francs per year—and the limited result. Instead, voluntary screening has been encouraged. France now has approximately 200 centers able to conduct screening and confirm results. The test, which requires a simple medical prescription, is reimbursed 65% by Social Security. Free and anonymous screening will soon be available in another 100 centers, with at least one center to serve each province.

With international travelers, the Health Ministry follows the recommendations of the World Health Organization and of the Council of European Health Ministers—no screening is undertaken at the border. An information brochure for French citizens leaving and foreigners entering the country is in preparation. The Ministry of Cooperation has developed a brochure for all its employees in foreign countries.

Finally, France, together with the World Health Organization, helps with the systematic screening of blood donors in the African countries requesting this program. In France, such screening is mandatory for all blood, organ, tissue, cell and sperm donors, as well as before any medically assisted procreation.

Training

Three types of training are currently available:

• High-level clinical training for hospital staff. This program is organized by the Claude Bernard Hospital, the World Health Organization, and the Health Ministry. Its goal, over the course of a week of training, is to familiarize the staff with taking care of AIDS patients, undertaking clinical and therapeutic research and becoming involved in local educational programs for AIDS.

• Training for people dealing with drug addicts. This program is aimed at improving the knowledge of AIDS among experts in drug addiction.

• Education in prisons. This program, directed and financed by the Ministry of Justice, is intended to train prison staff so that they in turn might become sources of information for inmates about AIDS prevention.

Monitoring and Treatment

At present most AIDS patients are cared for in hospitals, these mostly in the Paris area. Eleven centers for AIDS information, treatment and monitoring have been created in 1987, six outside Paris. More will be established in 1988. In these centers, AIDS patients are triaged to the different hospital services according to the patients' clinical manifestations. Those needing to be followed daily are placed in a day hospital of eight to ten beds.

Centralized laboratories equipped to handle the immunologic and virologic examination of AIDS patients have been established.

The information from the different centers and hospitals handling AIDS patients is centralized for statistical and epidemiologic studies under the direction of the National Institute for Health and Medical Research.

Research

The Director's Council of the National Program for AIDS Research, presided over by the Ministry of Research, deals mainly with these areas of investigation: molecular and cellular biology and viral multiplication, immunology, diagnosis, therapeutics, epidemiology and clinical research. Fifty teams of scientists, with a budget of 100 million francs, have been assembled. In addition, the Pasteur Institute's resources have been increased, and a new research center is being created for the study of molecules, with other centers being planned.

International Cooperation

Early on, France realized what an important role the World Health Organization was going to play in the control of the AIDS epidemic. It has taken part with the World Health Organization in the anti-AIDS program for the French-speaking African nations desiring assistance. It has also established bonds of cooperation with its American partners, with the help of the agreement between the Pasteur Institute and the National Institutes of Health in the United States.

Conclusion

The policy undertaken by France in the field of prevention and control of AIDS was a medium-range policy. It mainly considered the ethical, scientific and socioeconomic aspects of the new viral infection.

The first priority was organizing the monitoring and medical treatment of seropositive persons and sick patients and to find the means to enable research and development. As for prevention, measures have been taken for screening and the widespread use of prophylactics, as well as stopping the use of used syringes.

The national information campaign has helped make the population more aware and has lessened the state of panic, but it now is necessary to act in a more selective manner, by preparing people able to give detailed information to the different high-risk groups and to teenagers. It will also be necessary to evaluate our progress as we reach a better knowledge of the infection and the population's reaction to it. These evaluations will have to be conducted with the utmost efficiency and in the most perfect respect of individual rights and the rules of ethics.

The World Health Organization's Global Strategy for the Prevention and Control of AIDS

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The magnitude of the human immunodeficiency virus (HIV) pandemic and its broad impact have been seriously underestimated and underappreciated. The Special Programme on AIDS (acquired immunodeficiency syndrome) of the World Health Organization (WHO) was created on February 1, 1987, as the architect and keystone of the global AIDS plan. The Special Programme on AIDS has designed the global strategy, has raised sufficient funds to begin implementing the strategy and, for this effort, has marshalled the support of every nation in the world. AIDS affects both the developing and the industrialized worlds; therefore, every country will need a national AIDS program. This is vital not only for national interests but also because ultimately AIDS cannot be stopped in any one country unless it is stopped in all countries. National AIDS programs are being rapidly established throughout the world with the technical and financial support of WHO's Special Programme on AIDS. At the global level, the Special Programme is responsible for strategic leadership, developing consensus, coordinating scientific research, exchanging information, assuring technical cooperation and mobilizing and coordinating resources. National AIDS committees have already been established in more than 150 countries and, by the end of 1988, the Special Programme will support every country in the world that requests collaboration.

(Mann JM: The World Health Organization's global strategy for the prevention and control of AIDS, *In* AIDS—A global perspective [Special Issue]. West J Med 1987 Dec; 147:732-734)

When the acquired immunodeficiency syndrome (AIDS) was first recognized in 1981, the disease appeared limited to a single nation and to a single group characterized by its sexual orientation. Today, as a result of extensive national and international collaborative research, the worldwide epidemic of the human immunodeficiency virus (HIV) and related retroviruses* is recognized to be an international health problem of extraordinary scope and unprecedented urgency (Table 1 and see Figure 2 in the article elsewhere in this issue, C. F. von Reyn, MD, and J. M. Mann, MD, MPH, "Global Epidemiology," pp 694-701). The consciousness of the global extent of AIDS has led to the emergence of a global conscience about the disease and to the realization that a worldwide effort will be required to stop it.

The World Health Organization (WHO) has a mandate to direct and coordinate international health work. In May 1986, citing "intensive international interest and concern" about AIDS, the 39th World Health Assembly formally approved the creation of an AIDS program within WHO. In November 1986, the Director-General of the World Health Organization announced that in the same spirit and with the same dedication that characterized WHO's global smallpox eradication program, WHO was now committed to the more urgent, difficult and complex challenge of global AIDS prevention and control. The Special Programme on AIDS was created in February 1987 as the architect and keystone of the global AIDS plan. The Special Programme has designed the global plan, has raised sufficient funds to begin implementing the plan and, for this effort, has marshalled the support of every nation in the world.

The magnitude of the HIV pandemic and its broad impact have been seriously underestimated and underappreciated. During the second half of 1986, however, a major shift of perspective and opinion occurred in many North American, European and African countries. For example, in the United Kingdom, France, Italy and the United States, statements by prominent health officials and dramatically increased financial commitments for AIDS-prevention programs testify to a growing awareness of the scope of the HIV problem at national levels. A three-part evolution in perspective regarding AIDS can be observed at the personal, national and international levels. The initial response to AIDS usually involves denial and an effort to minimize the problem, often through comparison of the number of AIDS cases with deaths from already well-described public health problems. Then, as the

*The name "human immunodeficiency virus" has replaced the earlier names for the AIDS virus. The related retroviruses include the lymphadenopathy-associated virus (LAV-II), the human T-lymphotropic virus (HTLV-IV) and other recently recognized retroviruses that are related to HIV, with or without evidence of immunosuppression or clinical disease. In this document, "HIV" stands for all of these viruses.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
WHO = World Health Organization

number of AIDS cases increases rapidly and estimates of the number of persons already infected with HIV in the population are publicized, the HIV problem commands further attention. Finally, once the virus's potential to involve major segments of the population, including those who may have previously considered themselves without risk, is recognized, the epidemic nature and urgency of the HIV situation generate political commitment and a willingness to act.

While the international HIV situation is dynamic, agreement exists on the fundamental concepts and principal components of global AIDS prevention and control. These fundamental concepts include the following:

- HIV infection is an international health problem.
- Infection with HIV is an adverse health outcome of profound personal, family and social importance.
- HIV infections threaten the limited gains in health that have been achieved in several areas of the developing world.
- Neither vaccine nor therapy for widespread use is likely to become available for at least several years.
- The HIV global effort will be long term and will likely last beyond our generation.
- HIV prevention and control programs must be integrated with primary health care.
- The HIV pandemic represents an unprecedented challenge to public health that mandates a response of equally unprecedented creativity, energy and resource.

The global plan has three objectives:

- To prevent HIV transmission.
- To take care of HIV-infected persons (to reduce morbidity and mortality associated with HIV infection).
- To unite national and international efforts for global AIDS control.

AIDS affects both developing and industrialized countries; therefore, every country will need a national AIDS program. This is vital not only for national interests, but also because ultimately AIDS cannot be stopped in any one country unless it is stopped in all countries.

At the national level, AIDS prevention and control first require the political will to recognize the problem and to establish a broadly representative national AIDS committee. This committee is entrusted with the responsibility to develop a national plan for AIDS control. An initial assessment of the extent of the AIDS virus infection in the country is essential. Epidemiologic surveillance and laboratory support for diagnosis and testing must then be established. Education for health workers at all levels is critical, for not only are they responsible for the care of people with AIDS, but they are vital sources of accurate information for the public. The following specific prevention programs should be implemented: prevent sexual transmission through education; prevent parenteral transmission by making blood and blood products safe, by preventing intravenous drug abuse and educating and treating intravenous drug abusers, and by ensuring that injection equipment and other skin-piercing instruments are always sterile, and prevent perinatal transmission.

Finally, a comprehensive national AIDS program must help those persons already infected with HIV and help them to protect others.

National AIDS programs are being rapidly established throughout the world with the technical and financial support of WHO's Special Programme on AIDS.

National AIDS committees have already been established in more than 150 countries. From February to October 1987, the Special Programme on AIDS has collaborated with more than 90 countries throughout the world, providing more than 250 technical support missions by epidemiologists, laboratory specialists, planners, educators and other health professionals. Using WHO guidelines, 58 countries have prepared written plans for national AIDS prevention and control. Uganda, Kenya, Tanzania, Rwanda and Ethiopia have completed medium-term (three- to five-year) plans and in collaboration with WHO have received pledges from bilateral and multilateral agencies for more than $19 million to implement these plans. In addition, this past year 15 laboratory workshops will have trained about 300 laboratory workers from 90 countries; these laboratorians will then train others in their country in the latest HIV laboratory diagnostic methods.

By the end of 1988, the Special Programme on AIDS will support every country in the world that requests this collaboration. With the implementation of national AIDS plans, the Special Programme will be closely involved in monitoring and evaluating the effectiveness of these efforts. Just as smallpox eradication became possible when an effective epidemiologically based strategy was developed, strategy development is crucial to global AIDS control.

At the global level, the Special Programme is responsible for strategic leadership, developing consensus, coordinating scientific research (biomedical, social, behavioral and epidemiologic), exchanging information, assuring technical cooperation and mobilizing and coordinating resources. WHO alerted the international community on the global scope of AIDS and has continued to provide vital exchanges of technical and policy information. During 1987, meetings held in Africa, Asia, Australia and countries of the Pacific Rim,

TABLE 1.—*Worldwide Cases of the Acquired Immunodeficiency Syndrome Reported to the World Health Organization (to Nov 1, 1987)*

Worldwide Cases, No	?	*Jun 79*	*Dec 79*	*Jun 80*	*Dec 80*	*Jun 81*	*Dec 81*	*Jun 82*	*Dec 82*	*Jun 83*	*Dec 83*	*Jun 84*	*Dec 84*	*Jun 85*	*Dec 85*	*Jun 86*	*Dec 86*	*Jun 87*	*Oct 87*	*Total*
Global by 6-month periods . . .	173	4	10	23	36	90	196	388	740	1,486	1,929	2,815	4,100	5,443	7,251	9,373	12,559	13,833	2,413	62,784
USA by 6-month periods . . .	12	4	9	19	32	86	180	363	648	1,221	1,588	2,444	3,189	4,366	5,429	6,516	7,332	7,060	348	40,845
Global cumulation		4	14	37	73	161	359	739	1,487	2,965	4,902	7,708	11,817	17,246	24,511	33,653	46,443	58,814	62,689	62,784

Europe and the Americas have each marked turning points in national and regional AIDS awareness and action.

The World Health Organization has accomplished the following:

- Developed consensus on key issues including international travel and AIDS, childhood immunization and HIV and standards for HIV screening programs.
- Issued guidelines on the counseling and management of HIV-infected persons and on educational strategies for AIDS control.
- Established a world bank for the collection and exchange of AIDS viruses and other key reagents.
- Identified cross-cultural research priorities, including risk behaviors, perceptions of and responses to AIDS and impacts of AIDS on social structures, especially families.
- Created a global AIDS data bank, starting with information on AIDS cases and on HIV-1 and HIV-2 seroprevalence data.
- Developed a model methodology for determining HIV seroprevalence in the developing world.
- Initiated regional and global AIDS information and materials exchange to ensure that the best models from and lessons learned in AIDS information and education programs are shared throughout the world.

International Coordination

The United States has played an essential role in support of the Special Programme on AIDS. From the first, the United States has provided financial and moral support. The unwavering commitment of the US government to WHO as the leader of global AIDS control, expressed in the declarations of the Venice summit, the World Health Assembly, and the United Nations General Assembly, has been most essential and appreciated.

The scientific work to master AIDS, like the disease itself, is now firmly and irrevocably international. In AIDS, there really is no such thing as purely local or even purely national research. Therefore, looking to the future, we must work to ensure that the fruits of that research—drugs for treatment and vaccine—will be made available to the entire world and not just to the wealthy nations.

The Special Programme on AIDS will need, from the United States and from many countries, continued commitment to a principle and support for its application. The principle is that global AIDS control requires global leadership and coordination. The practical outcomes of this principle include ensuring that scientific and public health activities at the international level undertaken by US agencies and institutions are closely coordinated with those of WHO and a willingness to invest resources in global research and control. This support must be assured to WHO, and bilateral support for research and for control work must be coordinated with WHO. The specific objective of the coordination is to ensure that bilateral efforts are consistent not only with the global strategy, but with AIDS plans and programs at the national level. This coordination must be proactive and strong, not retroactive and desultory.

If AIDS had appeared 50 years ago, we would have been nearly defenseless against it—science would not yet have been able to define the cause, develop diagnostic and screening methods and progress so rapidly towards treatment and prevention through vaccine. Yet, there are at least three other ways in which today's world is much better armed and equipped to combat AIDS.

First, the concept and infrastructure of primary health care is now well established throughout the world. Primary health care delivers basic and fundamental health services to people where they live. Just as critical for AIDS prevention is the health promotion philosophy that stresses the capacity and responsibility of persons and communities to prevent the disease through information and education leading to changes in individual and collective behavior.

The second major factor is the development of modern social and behavioral science, which we are now applying to design efficient and socially acceptable public health information and education strategies.

The third factor is the emergence of a global conscience expressed concretely in the foreign assistance programs of the world and through the establishment of the United Nations with its specialized agencies such as the World Health Organization.

WHO considers AIDS to be an inescapable priority; we cannot give AIDS a "grace period." A worldwide effort will stop it.

Appendices

Appendix I

Special Programme on AIDS and Expanded Programme on Immunization—Joint Statement

Consultation on Human Immunodeficiency Virus (HIV) and Routine Childhood Immunization

Concern has been raised that children infected with the human immunodeficiency virus (HIV) who receive routine childhood immunizations may have decreased immune responses and be at increased risk for adverse effects or acceleration of HIV-induced immunosuppression. Limited experience suggests that the likelihood of successful immunization is reduced in some HIV-infected individuals, but that the risk of serious adverse effects remains low. The theoretical risk of accelerating HIV infection by simultaneous administration of multiple antigens is not supported by limited clinical information and is likely to be negligible in contrast to other natural sources of antigenic stimulation.

Having reviewed the available information in Geneva on August 12 and 13, 1987, the World Health Organization's informal consultation on HIV and routine childhood immunization

1. Endorses the 1986 Expanded Programme on Immunization (EPI) Global Advisory Group recommendations on the use of EPI antigens:

   In countries where human immunodeficiency virus (HIV) infection is considered a problem, individuals should be immunized with the EPI antigens according to standard schedules. This also applies to individuals with asymptomatic HIV infection. Unimmunized individuals with clinical (symptomatic) AIDS in countries where the EPI target diseases remain serious risks should not receive bacille Calmette Guérin (BCG), but should receive the other vaccines (Table 1).

TABLE 1.—*Recommendations on the Use of EPI Antigens in HIV-Infected Individuals in Countries Where the EPI Target Diseases Remain Important Causes of Morbidity*

	Vaccine	*Asymptomatic*	*Clinical AIDS*
Infants	BCG	Yes	No
	DTP	Yes	Yes
	OPV	Yes	Yes
	IPV	Yes	Yes
	Measles	Yes	Yes
Women	Tetanus toxoid	Yes	Yes

2. In accordance with the Global Advisory Group, notes that live vaccines are not usually given to immunocompromised individuals, but agrees that, in areas where the risk of exposure to measles and poliovirus is high, the benefits of immunization outweigh the apparently low risk of adverse effects from these vaccines, even in the presence of symptomatic HIV infection. Inactivated poliomyelitis vaccine (IPV) is an alternative to oral poliomyelitus vaccine (OPV) for immunization of children with symptomatic HIV infection who may be at increased risk of OPV-associated paralytic poliomyelitis.
3. Notes that although a theoretical risk exists, evidence for an increased rate of adverse reactions after BCG immunization among asymptomatic HIV-infected individuals remains inconclusive. Therefore,
   (a) For asymptomatic HIV-infected individuals:
   - Where the risk of tuberculosis is high, BCG is recommended at birth or as soon as possible thereafter in accordance with standard policies for immunization of non-HIV-infected children;
   - In a limited number of areas, the risk of tuberculosis is low, but BCG is recommended as a routine immunization; in these areas, BCG may be withheld from individuals known or suspected to be infected with HIV;

   (b) For symptomatic HIV-infected individuals, BCG should be withheld.
4. Emphasizes the EPI recommendation to immunize children as early in life as possible. Vaccine-associated adverse effects may be minimized and vaccine response optimized by beginning immunization before the progression of HIV-induced immunosuppression.
5. Endorses the simultaneous administration of multiple antigens such as BCG, DTP, polio and measles vaccines when indicated.
6. Strongly encourages further investigations in the following areas:
   (a) Safety of immunizations in HIV-infected children:
   - Surveillance of HIV-infected children to permit the rapid identification of any unexpectedly frequent adverse events following immunization;
   - Establishing or modifying population-based surveillance systems to detect rare serious adverse events associated with the immunization of HIV-infected children;
   - Comparing the rates of frequent and less severe adverse events that occur in HIV-infected and uninfected children following immunization.

   (b) The natural history of vaccine-preventable diseases in HIV-infected children:
   - Determining the rates of serious complications of vaccine-preventable diseases in HIV-infected children in health care facilities and in the community and correlating such complications with the stage of HIV infection and degree of immunosuppression;
   - Establishing or modifying population-based surveillance systems to detect serious complications of vaccine-preventable diseases in HIV-infected children;
   - Assessing the role of immune globulin in protecting HIV-infected children against vaccine-preventable diseases.

   (c) Immunogenicity and efficacy of immunizations in HIV-infected children:
   - Determining the serologic response to immunization in HIV-infected children compared with uninfected children and correlating vaccine response to the stage of HIV infection and the degree of immunosuppression;
   - Developing methods to improve vaccine responses of HIV-infected children, if these are found to be decreased;
   - Determining the persistence of vaccine-induced antibody;
   - Prospectively observing immunized HIV-infected children and retrospectively evaluating cases of vaccine-preventable diseases to determine rates of vaccine failure in HIV-infected children.

   (d) Possible activation or acceleration of HIV infection by repeated antigenic stimulation with immunizations, including the simultaneous administration of multiple antigens:
   - Detecting increased HIV replication following immunization of HIV-infected children;
   - Detecting immunologic abnormalities following immunization of HIV-infected children;
   - Retrospectively studying the relationship between the total number of immunizations or of antigens (or both) received simultaneously by HIV-infected children and the onset of symptomatic HIV infection, progression of clinical HIV disease or fatal outcome of HIV infection. In the informal consultation, it was agreed that prospective placebo-controlled double-blind studies in which some HIV-infected children would not receive recommended immunizations are not appropriate.

   (e) The immunogenicity and efficacy of tetanus toxoid immunization of HIV-infected pregnant women in the prevention of neonatal tetanus.

Special Programme on AIDS Statement—Criteria for Screening Programs for Human Immunodeficiency Virus (HIV)

Screening for infection or disease has been a useful activity in a variety of public health programs. Screening programs, however, must be carefully considered and well designed to contribute effectively to public health goals.

Programs of screening for infection with the human immunodeficiency virus (HIV) have been proposed in various countries. In many countries, for example, screening of blood donors has been successfully imple-

mented. However, the purpose and objectives of some HIV screening programs may not have been clearly defined, and the complex logistic, technical, economic, legal, ethical and social aspects of such programs may not have been addressed and resolved. Inadequately designed HIV screening programs may be intrusive, may even threaten fundamental human rights and are very likely to be both expensive and ineffective. Further, such programs may have a negative effect on AIDS prevention and control by diverting human, material and financial resources away from education programs and other vital HIV-prevention activities.

To help ensure that these issues are systematically addressed whenever HIV screening programs are considered, the WHO Special Programme on AIDS convened a meeting on "Criteria for HIV-Screening Programs" in Geneva on May 20-21, 1987. In all, 21 participants from 17 countries attended the meeting, including epidemiologists, virologists, experts in legal medicine and ethics, social and behavioral scientists and disease control specialists.

At the meeting, a comprehensive list of criteria was developed, which should be explicitly addressed in the planning of any HIV screening program. By adhering to these criteria, successful and effective public health results from any screening programs can best be ensured. The interests of public health and respect for human rights will best be served by addressing all of these criteria with care before initiating screening programs that are an element in HIV prevention and control strategies. Conversely, any HIV screening program that fails to address these criteria must be considered to be inadequate.

These criteria include more than 50 distinct issues that are grouped under 9 headings:

1. *What is the rationale of the proposed program?*
2. *What population is to be screened?*

   How will persons in the target population be identified for screening?

   If testing is obligatory, what sanctions would apply if persons fail to comply?

   What is the plan for periodic retesting of the population screened?
3. *What test method is to be used?*

   Problem of false-positive test results, technical aspects and limitations of test.

   Technical skill and training required by technicians.

   Storage characteristics and stability of reagents.

   Interpretation characteristics of the test.
4. *Where is the laboratory testing to be done?*

   Are quality control systems adequate for tests and procedures?
5. *What is the intended disposition of data obtained from testing?*

   How will confidentiality be assured?

   Under what conditions will individuals, other than the person tested, be permitted to seek and obtain access to the data?
6. *What plan will be used for communicating results to the person tested?*

   Who will transmit the information?

   If test results cannot be conveyed in person, how will the information be conveyed?

   Other than the person tested, who is to be informed of the test result?
7. *How is counseling to be accomplished?*

   Who will counsel?

   How will counselors be trained and the adequacy of their performance be assured?

   Where will counseling services be provided?
8. *What is the social impact of screening?*

   Will persons who are tested be deprived of legal or social rights that otherwise are protected?

   Are appropriate supplemental laboratory test procedures used to minimize false-positive results that are an inevitable part of screening tests?

   Persons falsely assumed to be seropositive also can suffer severe and unjust adverse consequences.
9. *What legal and ethical considerations are raised by the proposed screening program?*

   Is informed consent required?

   Are statutes or regulations in place that safeguard against breaches of confidentiality or intentional disclosure of personal information that is not necessary for public health purposes?

The Special Programme on AIDS will provide consultation on the criteria and their application on request from member states.

Special Programme on AIDS Statement

Breast-feeding/Breast Milk and Human Immunodeficiency Virus (HIV)

In view of the importance of breast milk and breast-feeding for the health of infants and young children, and of the increasing prevalence of human immunodeficiency virus (HIV) infection in many parts of the world, a Consultation on Breast-feeding/Breast Milk and HIV Infection was organized by the Special Programme on AIDS and the Division of Family Health on June 23-25, 1987. Its purpose was to review currently available information on the possible relationship between breast-feeding, breast milk and HIV transmission and to identify further research needs in this area. Twenty participants from 15 countries attended the consultation. The participants represented epidemiology, immunology, virology, pediatrics and nutrition. The conclusions of the consultation are summarized below.

Evidence concerning the transmission of HIV from infected mothers to their infants suggests that between 25% and 50% of all offspring will be infected. The risk of transmission may depend on a number of factors, including the timing of the mother's HIV infection, the mother's immunologic and overall health status, her parity and intercurrent infections and other possible factors.

Transmission of HIV from infected mothers to their infants may occur before, during or shortly after birth. The possibility that HIV could be transmitted through breast-feeding or breast milk is supported by a report that HIV can be cultured from breast milk from mothers who are themselves infected. At present, the risk of HIV transmission from mothers to infants through breast-feeding has not been defined, but available information suggests that if such transmission occurs, the relative contribution of this route is probably small, as compared with in utero and intrapartum transmission. For example, a substantial number of infants born to infected mothers have been breast-fed without their having any evidence of HIV infection. On the other hand, there are a few reported cases where mothers became infected postpartum through blood transfusions and where their infants, in turn, became infected, possibly through breast-feeding. This does not necessarily imply, however, that such transmission occurs among mothers who were infected with HIV before or during pregnancy.

Additional epidemiologic and laboratory research is needed on the risks of HIV transmission through breast milk and on the potential benefits of breast milk in situations where infants have been exposed to HIV or are already infected.

In the interim,

- Breast-feeding should continue to be promoted, supported and protected in both developing and developed countries. The overall immunologic, nutritional, psychosocial and child-spacing benefits of breast-feeding to infants and their mothers continue to be important factors in determining the overall health of mother and child.
- If, for whatever reason, the biological mother cannot breast-feed or her milk is not available, and the use of pooled human milk is considered, the report of the isolation of HIV in breast milk should be taken into account. Pasteurization at 56°C for 30 minutes has been reported to inactivate the virus. Further research on the effectiveness of different methods of pasteurization, however, is needed. As an additional precaution, the possibility of screening donors (in accordance with WHO criteria on HIV screening) should be considered, especially in areas where the prevalence of HIV infection is known to be high. Similarly, if, for whatever reason, the biological mother cannot breast-feed, or her milk is not available, and where wet-nursing is the next obvious choice, care may need to be taken in selecting the wet-nurse, bearing in mind her possible HIV infection status and that of the infant who is to be fed.
- In individual situations where the mother is considered to be HIV-infected, and recognizing the difficulties inherent in assessing the infection status of the newborn, the known and potential benefits of breast-feeding should be compared with the theoretical, but apparently small, incremental risk to the infant of becoming infected through breast-feeding. Consideration should be given to the socioeconomic and ecologic environment of the mother-child pair and the extent to which alternatives can safely and effectively be used. In many circumstances and particularly where the safe and effective use of alternatives is not possible, breast-feeding by the

biological mother should continue to be the feeding method of choice, irrespective of her HIV infection status.

World Health Organization—Special Programme on AIDS

Consultation on International Travel and Human Immunodeficiency Virus (HIV)

A consultation on international travel and human immunodeficiency virus (HIV) was convened by the World Health Organization's Special Programme on AIDS on March 2-3, 1987, in Geneva.

The consultation addressed three related issues:

- HIV screening of international travelers,
- Travel of HIV-infected persons by public conveyance,
- Recommendations for international travelers on the prevention of HIV infection.

1. The consultation concluded that, at best and at great cost, HIV screening of international travelers would retard only briefly the spread of HIV, both globally and with respect to any particular country.

   The AIDS epidemic is now global; 91 countries from all regions of the world have reported AIDS cases to WHO (see Appendices 2 and 3), and virtually all nations are already involved, at least to some extent, in the HIV pandemic.

   Therefore, the only possible rationale for HIV screening of international travelers would be an effort to slow, rather than to prevent, the spread of HIV.

   Serious logistic, epidemiologic, economic, legal, political and ethical problems are inherent in any proposal for HIV screening of international travelers. For example, no screening system can prevent the introduction and spread of HIV infection; a program for screening of international travelers would have to involve nationals returning from travel abroad as well as foreign entrants.

   The diversion of resources to HIV screening of international travelers and away from educational programs and measures to protect the blood supply is not justified. Rather than screening, the consultation would recommend education programs directed to both national and international travelers.

2. The consultation concluded that the use of any public conveyance—such as train, bus, airplane, car, ship—by persons infected with HIV does not create a risk of infection for others sharing the same conveyance. Therefore, there is no reason to limit the use of public conveyances by HIV-infected persons.

3. Recommendations for international travelers on prevention of HIV infection:

   The routes of HIV transmission have been documented to be the same throughout the world. Therefore, the behaviors that put individuals at risk of acquiring HIV are similar worldwide. Preventive measures against HIV are also the same worldwide, regardless of whether a person is a traveler or a resident of a given country.

   Educational materials should be made available for international travelers to increase awareness of how HIV is transmitted and how it can be prevented. This educational material should indicate specific preventive measures in clear, easily understood language. This involves a difficult balance because the transmission of HIV is primarily sexual and therefore involves many social and cultural sensitivities. It is essential, however, to discuss these sensitive issues openly to protect international travelers.

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Appendix 2

AIDS Cases Reported to WHO

Summary of AIDS Cases Reported to WHO as of 21 Oct 87

Continent	Number of Cases	Number of Countries or Territories Reporting to WHO	Zero Cases	1 or More Cases
Africa	5,830	46	10	36
Americas	48,257	44	3	41
Asia	205	26	8	18
Europe	7,475	28	1	27
Oceania	678	13	9	4
Total	62,445	157	31	126

WHO Region	Number of Cases	Number of Countries or Territories Reporting to WHO
African	5,815	42
American	48,257	44
Eastern Mediterranean	66	8
European	7,538	30
Southeast Asian	23	10
Western Pacific	746	23
Total	62,445	157

AIDS Cases Reported to WHO by 6-Month Period (21 Oct 87)

Country	?	Jun 79	Dec 79	Jun 80	Dec 80	Jun 81	Dec 81	Jun 82	Dec 82	Jun 83	Dec 83	Jun 84	Dec 84	Jun 85	Dec 85	Jun 86	Dec 86	Jun 87	Dec 87	Total
Africa	0	0	0	0	0	0	0	0	3	2	12	6	76	5	180	986	2,125	2,328	107	5,830
Americas	172	4	10	23	32	89	184	376	677	1,433	1,750	2,585	3,651	4,778	6,115	7,175	8,384	8,967	1,852	48,257
Asia	0	0	0	0	1	0	0	0	1	0	8	0	4	11	18	10	44	75	33	205
Europe	14	0	0	0	3	1	12	11	58	52	163	212	361	554	787	1,013	1,464	2,367	403	7,475
Oceania	0	0	0	0	0	0	0	0	1	1	5	6	39	68	56	98	141	186	77	678
Total	186	4	10	23	36	90	196	387	740	1,488	1,938	2,809	4,131	5,416	7,156	9,282	12,158	13,923	2,472	62,445

AIDS Cases Reported to WHO by Year (21 Oct 87)

Continent	?	1979	1980	1981	1982	1983	1984	1985	1986	1987	Total
Africa	0	0	0	0	3	14	82	185	3,111	2,435	5,830
Americas	172	14	55	273	1,053	3,183	6,236	10,893	15,559	10,819	48,257
Asia	0	0	1	0	1	8	4	29	54	108	205
Europe	14	0	3	13	69	215	573	1,341	2,477	2,770	7,475
Oceania	0	0	0	0	1	6	45	124	239	263	678
Total	186	14	59	286	1,127	3,426	6,940	12,572	21,440	16,395	62,445

Cumulative Number of Cases (21 Oct 87)

Continent	1979	1980	1981	1982	1983	1984	1985	1986	1987	?	Total
Africa	0	0	0	3	17	99	284	3,395	5,830	0	5,830
Americas	14	69	342	1,395	4,578	10,814	21,707	37,266	48,085	172	48,257
Asia	0	1	0	2	10	14	43	97	205	0	205
Europe	0	3	16	85	300	873	2,214	4,691	7,461	14	7,475
Oceania	0	0	0	1	7	52	176	415	678	0	678
Total	14	73	359	1,486	4,912	11,852	24,424	45,864	62,259	186	62,445

AIDS Cases Reported to WHO by Countries and Territories in Africa by 6-Month Period (21 Oct 87)

Country	*Dec 82*	*Jun 83*	*Dec 83*	*Jun 84*	*Dec 84*	*Jun 85*	*Dec 85*	*Jun 86*	*Dec 86*	*Jun 87*	*Dec 87*	*Total*
Algeria	..	..	..	..	..	..	..	3	..	2	..	5
Angola	..	..	..	..	..	..	3	..	3	..	..	6
Benin	..	..	..	..	..	..	..	..	2	1	..	3
Botswana	..	..	..	..	..	..	1	1	4	6	1	13
Burkina Faso	..	..	..	..	..	..	..	..	0	..	..	0
Burundi	..	..	..	..	..	..	..	..	..	128	..	128
Cameroon	..	..	..	..	..	..	..	..	21	4	..	25
Cape Verde	..	..	..	..	..	..	1	1	..	2	..	4
Central African Republic	..	..	..	1	..	..	..	157	96	..	..	254
Chad	..	..	..	..	..	..	..	..	1	..	..	1
Comoros	..	..	..	..	..	..	..	0	0	..	..	0
Congo	..	..	..	..	..	..	..	..	250	..	..	250
Cote d'Ivoire	..	..	..	..	..	..	..	..	118	..	..	118
Djibouti	..	..	..	..	..	..	..	..	..	..	0	0
Egypt	..	..	..	..	..	..	..	..	..	1	..	1
Ethiopia	..	..	..	..	..	..	..	0	0	5	..	5
Gabon	..	..	..	..	..	..	..	..	0	13	..	13
Gambia	..	..	..	..	..	..	..	0	0	14	..	14
Ghana	..	..	..	..	..	..	..	7	66	72	..	145
Guinea	..	..	..	..	..	..	..	..	0	9	..	9
Guinea-Bissau	..	..	..	..	..	..	..	..	0	2	..	2
Kenya	..	..	..	..	..	..	10	91	8	421	95	625
Lesotho	..	..	..	..	..	..	..	..	1	..	..	1
Liberia	..	..	..	..	..	..	..	..	0	2	..	2
Madagascar	..	..	..	..	..	..	..	..	0	..	..	0
Malawi	..	..	..	..	..	..	..	..	13	..	..	13
Mali	..	..	..	..	..	..	..	..	..	..	0	0
Mauritania	..	..	..	..	..	..	..	..	0	..	..	0
Mauritius	..	..	..	..	..	..	..	0	0	1	..	1
Mozambique	..	..	..	..	..	..	..	..	1	0	..	1
Nigeria	..	..	..	..	..	..	..	0	0	5	..	5
Reunion	..	..	..	..	..	..	..	0	0	1	..	1
Rwanda	..	..	10	..	73	..	161	..	461	..	..	705
Sao Tome/Principe	..	..	..	..	..	..	..	..	0	..	..	0
Senegal	..	..	..	..	..	..	..	..	0	..	..	0
Seychelles	..	..	..	..	..	..	..	..	0	..	..	0
South Africa	3	2	2	5	3	5	4	10	21	22	4	81
Sudan	..	..	..	..	..	..	..	..	..	5	7	12
Swaziland	..	..	..	..	..	..	..	..	1	6	..	7
Tanzania	..	..	..	..	..	..	..	462	237	431	..	1,130
Togo	..	..	..	..	..	..	..	..	0	..	..	0
Tunisia	..	..	..	..	..	..	..	2	..	..	..	2
Uganda	..	..	..	..	..	..	..	29	737	372	..	1,138
Zaire	..	..	..	..	..	..	..	..	..	335	..	335
Zambia	..	..	..	..	..	..	..	217	33	145	..	395
Zimbabwe	..	..	..	..	..	..	..	6	51	323	..	380
Africa	3	2	12	6	76	5	180	986	2,125	2,328	107	5,830

AIDS Cases Reported to WHO by Countries and Territories in the Americas by 6-Month Period (21 Oct 87)

Country	?	Jun 79	Dec 79	Jun 80	Dec 80	Jun 81	Dec 81	Jun 82	Dec 82	Jun 83	Dec 83	Jun 84	Dec 84	Jun 85	Dec 85	Jun 86	Dec 86	Jun 87	Dec 87	Total
Anguilla	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	..	0	..	0
Antigua	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	0	1	..	3
Argentina	..	..	..	..	..	..	..	..	..	..	6	2	3	15	16	16	11	9	34	112
Bahamas	..	..	..	..	..	..	..	..	..	..	..	..	..	2	36	30	17	20	..	105
Barbados	..	..	..	..	..	..	..	..	..	..	..	..	..	..	4	..	11	29	..	44
Belize	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..	2
Bermuda	..	..	..	..	..	..	..	..	..	..	..	..	5	5	17	15	6	15	..	63
Bolivia	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	0	..	1	..	2
Brazil	91	..	..	..	..	..	..	..	6	9	35	34	104	136	125	199	243	713	318	2,013
Br Virgin Islands	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	0	..	..	0
Canada	1	..	1	3	..	3	2	8	14	28	24	61	77	130	177	195	215	61	..	1,000
Cayman Islands	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	1	1	..	2
Chile	..	..	..	..	..	..	..	..	..	..	..	..	4	2	4	7	5	6	14	42
Colombia	..	..	..	..	..	..	..	..	..	..	..	4	0	1	9	..	16	27	96	153
Costa Rica	..	..	..	..	..	..	..	..	..	..	2	2	2	0	3	3	4	15	..	31
Cuba	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	2	2	5
Dominica	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	..	5	..	5
Dominican Republic	..	..	..	..	..	..	..	0	1	1	2	1	3	14	17	23	34	104	..	200
Ecuador	..	..	..	..	..	..	..	..	..	..	..	..	..	..	4	3	..	11	34	52
El Salvador	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	4	6	..	12
French Guiana	..	..	..	..	..	..	..	..	..	2	1	2	1	9	16	..	27	..	..	58
Grenada	..	..	..	..	..	..	..	..	..	..	..	2	..	..	0	..	1	2	..	5
Guadeloupe	..	..	..	..	..	..	..	1	1	1	..	4	2	4	3	7	17	..	..	40
Guatemala	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	5	8	12	..	27
Guyana	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	0	1	..	1
Haiti	..	..	..	..	..	..	..	..	..	157	75	..	211	..	126	..	242	40	61	912
Honduras	..	..	..	..	..	..	..	..	..	..	..	..	..	1	2	3	7	16	..	29
Jamaica	..	..	..	..	..	..	..	..	..	..	2	..	..	0	2	1	1	13	..	19
Martinique	..	..	..	..	..	..	..	..	..	..	1	1	2	2	2	2	6	9	..	25
Mexico	68	..	..	1	..	..	1	2	6	14	6	14	30	40	59	66	37	190	..	534
Montserrat	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	..	0	..	0
Nicaragua	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	0	0	19	19
Panama	..	..	..	..	..	..	..	..	..	..	..	..	1	2	1	5	3	2	8	22
Paraguay	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	1	13	..	14
Peru	..	..	..	..	..	..	..	1	..	..	..	2	2	4	0	0	..	..	35	44
St Christopher	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	0	..	..	1
St Lucia	..	..	..	..	..	..	..	..	..	..	..	..	1	..	2	0	0	..	..	3
St Vincent	..	..	..	..	..	..	..	..	..	..	..	..	..	1	2	0	0	..	..	3
Suriname	..	..	..	..	..	..	..	..	..	..	..	1	0	1	0	0	..	3	..	5
Trinidad & Tobago	..	..	..	..	..	..	..	..	..	1	8	7	..	24	31	37	26	44	..	178
Turks & Caicos	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	2	..	4
United States America	12	4	9	19	32	86	181	364	649	1,220	1,586	2,447	3,194	4,368	5,442	6,546	7,408	7,588	1,199	42,354
Uruguay	..	..	..	..	..	..	..	..	..	..	2	1	0	1	2	1	1	5	..	13
Venezuela	..	..	..	..	..	..	..	..	..	..	..	..	9	15	8	8	29	..	32	101
Americas	172	4	10	23	32	89	184	376	677	1,433	1,750	2,585	3,651	4,778	6,115	7,175	8,384	8,967	1,852	48,257

AIDS Cases Reported to WHO by Countries and Territories in Asia by 6-Month Period (21 Oct 87)

Country	*Dec 80*	*Jun 81*	*Dec 81*	*Jun 82*	*Dec 82*	*Jun 83*	*Dec 83*	*Jun 84*	*Dec 84*	*Jun 85*	*Dec 85*	*Jun 86*	*Dec 86*	*Jun 87*	*Dec 87*	*Total*
Bangladesh	..	..	..	..	..	..	..	..	..	..	..	..	0	0	..	0
Bhutan	..	..	..	..	..	..	..	..	..	..	..	..	0	0	..	0
Brunei Darussalam	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	0
Burma	..	..	..	..	..	..	..	..	..	..	..	..	0	0	..	0
China	..	..	..	..	..	..	..	..	..	..	1	..	..	1	..	2
China (Taiwan)	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	1
Cyprus	..	..	..	..	..	..	..	..	..	..	..	1	0	2	..	3
Eastern Med Region	..	..	..	..	..	..	..	..	..	..	..	..	6	7	23	36
Hong Kong	..	..	..	..	..	..	..	..	..	3	0	0	0	1	..	4
India	..	..	..	..	..	..	..	..	..	..	0	2	3	4	..	9
Indonesia	..	..	..	..	..	..	..	..	..	..	0	0	0	1	..	1
Israel	1	..	..	..	1	..	8	..	2	..	3	..	19	5	3	42
Japan	..	..	..	..	..	..	..	..	..	6	5	5	9	18	7	50
Korea, DPR	..	..	..	..	..	..	..	..	..	..	..	..	..	0	..	0
Korea, Rep	..	..	..	..	..	..	..	..	..	..	..	0	0	1	..	1
Lebanon	..	..	..	..	..	..	..	..	..	..	..	..	..	3	..	3
Malaysia	..	..	..	..	..	..	..	..	..	..	..	..	1	0	..	1
Maldives	..	..	..	..	..	..	..	..	..	..	0	..	0	0	..	0
Nepal	..	..	..	..	..	..	..	..	..	..	..	..	0	0	..	0
Philippines	..	..	..	..	..	..	..	..	..	..	1	..	2	4	..	7
Qatar	..	..	..	..	..	..	..	..	..	..	..	..	..	9	..	9
Singapore	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..	2
Sri Lanka	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..	2
Thailand	..	..	..	..	..	..	..	..	2	2	2	0	0	5	..	11
Turkey	..	..	..	..	..	..	..	..	..	..	6	1	2	12	..	21
Viet Nam	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	0
Asia	1	..	..	..	1	..	8	..	4	11	18	10	44	75	33	205

AIDS Cases Reported to WHO by Countries in Europe by 6-Month Period (21 Oct 87)

Country	?	Jun 79	Dec 79	Jun 80	Dec 80	Jun 81	Dec 81	Jun 82	Dec 82	Jun 83	Dec 83	Jun 84	Dec 84	Jun 85	Dec 85	Jun 86	Dec 86	Jun 87	Dec 87	Total
Albania	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	0
Austria	..	.	..	..	..	..	..	..	..	..	..	..	13	5	10	8	18	39	..	93
Belgium	.	..	..	..	..	..	..	..	21	..	33	24	25	26	32	19	36	39	..	255
Bulgaria	..	..	..	..	..	..	..	..	..	..	..	..	..		..	0	0	1	2	3
Czechoslovakia	..	..	..	..	..	..	..	..	..	..	..	..	..	.	..	4	2	1	..	7
Denmark	..	..	..	..	1	1	1	2	2	6	6	10	7	14	22	20	39	45	..	176
Federal Republic Germany	14	..	..	..	2	0	0	5	6	22	17	41	75	114	171	206	269	334	124	1,400
Finland	..	..	..	..	..	..	..	..	..	..	..	..	5	1	4	1	3	5	..	19
France	..	..	..	..	..	..	7	..	20	..	57	77	99	139	174	286	362	759	..	1,980
German Democratic Republic	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	1	3	..	4
Greece	..	..	..	..	..	..	..	..	..	..	1	1	4	3	4	9	13	14	..	49
Hungary	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	4	..	5
Iceland	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	2	0	..	4
Ireland	..	..	..	..	..	..	..	..	..	..	..	..	..	..	8	2	4	5	..	19
Italy	..	..	..	..	..	..	..	1	..	2	2	8	15	74	102	175	229	348	69	1,025
Luxembourg	..	..	..	..	..	..	..	..	..	..	..	..	..	1	2	1	2	1	..	7
Malta	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	5	0	1	..	6
Netherlands	..	..	..	..	..	..	..	1	2	6	9	6	24	28	31	50	73	78	..	308
Norway	..	..	..	..	..	..	..	..	..	..	..	..	5	6	6	7	11	14	..	49
Poland	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..	2
Portugal	..	..	..	..	..	..	..	..	..	..	1	1	..	6	11	9	18	21	..	67
Romania	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	1	0	..	2
Spain	..	..	..	..	..	..	1	1	1	5	5	11	13	34	59	47	87	244	..	508
Sweden	..	..	..	..	..	..	..	..	..	3	3	2	8	13	17	11	37	35	10	139
Switzerland	..	..	..	..	..	..	3	..	4	..	11	10	12	23	37	38	54	74	..	266
United Kingdom	..	..	..	..	..	..	..	1	2	8	18	21	56	67	93	113	195	296	197	1,067
USSR	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	1	2	1	4
Yugoslavia	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	1	5	3	..	11
Europe	14	..	..	..	3	1	12	11	58	52	163	212	361	554	787	1,013	1,464	2,367	403	7,475

AIDS Cases Reported to WHO by Countries and Territories in Oceania by 6-Month Period (21 Oct 87)

	Dec 82	Jun 83	Dec 83	Jun 84	Dec 84	Jun 85	Dec 85	Jun 86	Dec 86	Jun 87	Dec 87	Total
Australia	1	1	5	6	36	62	51	93	127	171	69	622
Cook Islands	..	..	..	..	..	..	..	..	..	..	0	0
Fiji	..	..	..	..	..	..	..	..	..	..	0	0
French Polynesia	..	..	..	..	..	..	..	..	..	1	..	1
Mariana Islands	..	..	..	..	..	..	..	..	..	..	0	0
New Caledonia	..	..	..	..	..	..	..	..	..	..	0	0
New Zealand	..	..	..	..	3	6	5	5	14	14	7	54
Papua New Guinea	..	..	..	..	..	..	..	..	..	..	0	0
Samoa	..	..	..	..	..	..	..	..	..	..	0	0
Solomon Islands	..	..	..	..	..	..	..	..	..	..	0	0
Tonga	..	..	..	..	..	..	..	..	..	..	1	1
Tuvalu	..	..	..	..	..	..	..	..	..	..	0	0
Vanuatu	..	..	..	..	..	..	..	..	0	0	0	0
Oceania	1	1	5	6	39	68	56	98	141	186	77	678

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Appendix 3

AIDS Cases Reported—By Country

Cases of the Acquired Immunodeficiency Syndrome Reported to World Health Organization as of 21 Oct 87

Continent	Country or Territory	Date of Report	Number of Cases	Source
Europe	Albania	31 Aug 87	0	Ministry of Health via DT, 31.8.87
Africa	Algeria	01 Jun 87	5	Ministry of Health, June 1987
Africa	Angola	26 Sep 86	6	AFRO Memo, 21.4.87
Americas	Anguilla	31 Mar 87	0	CAREC Surv. Rpt. 87/4
Americas	Antigua	30 Jun 87	3	CAREC Report, 17.9.87
Americas	Argentina	18 Sep 87	112	AMRO, 18.9.87
Oceania	Australia	05 Oct 87	622	AIDS cum.analys. cases 5.10.87
Europe	Austria	30 Jun 87	93	WHO Coll Ctr AIDS, Paris 1.9.87
Americas	Bahamas	31 Mar 87	105	CAREC Report, 17.9.87
Asia	Bangladesh	14 Apr 87	0	SEARO 14.4.87
Americas	Barbados	30 Jun 87	44	CAREC Report, 17.9.87
Europe	Belgium	30 Jun 87	255	WHO Coll Ctr AIDS, Paris, 1.9.87
Americas	Belize	30 Jun 87	2	AMRO, 18.9.87
Africa	Benin	18 May 87	3	Ministry of Health via AFRO Memo 10.7.87
Americas	Bermuda	30 Jun 87	63	CAREC Report, 17.9.87
Asia	Bhutan	14 Apr 87	0	SEARO 14.4.87
Americas	Bolivia	18 Sep 87	2	AMRO, 18.9.87
Africa	Botswana	30 Jun 87	13	Dept Epidemiology, 10.7.87
Americas	Brazil	15 Sep 87	2,013	AMRO, 18.9.87
Asia	Brunei Darussalam	08 Sep 87	0	WPRO Memo, 8.9.87
Americas	Br Virgin Islands	31 Dec 86	0	WER No. 16, 17.4.87
Europe	Bulgaria	06 Oct 87	3	Ministry of Health, 6.10.87*
Africa	Burkina Faso	13 Nov 86	0	AIDS Conf Brazzaville, 13.11.86
Asia	Burma	14 Apr 87	0	SEARO 14.4.87
Africa	Burundi	31 Mar 87	128	Ministry of Health, 27.5.87
Africa	Cameroon	05 Mar 87	25	National AIDS Committee, 5.3.87
Americas	Canada	27 Apr 87	1,000	'AIDS' in Canada, 27.4.87
Africa	Cape Verde	30 Apr 87	4	Ministry of Health, 30.4.87
Americas	Cayman Islands	31 Mar 87	2	CAREC Report, 17.9.87
Africa	Central African Republic	31 Oct 86	254	AFRO Memo, 10.7.87
Africa	Chad	13 Nov 86	1	AIDS Conf Brazzaville, 13.11.86
Americas	Chile	30 Jun 87	42	AMRO, 18.9.87
Asia	China	08 Sep 87	2	WPRO Memo, 8.9.87
Asia	China (Taiwan)	26 Jan 86	1	Epidemiol Bull. 86/4, 15.4.86
Americas	Colombia	01 Sep 87	153	AMRO, 18.9.87
Africa	Comoros	13 Nov 86	0	AIDS Conf Brazzaville, 13.11.86
Africa	Congo	13 Nov 86	250	AIDS Conf Brazzaville, 13.11.86
Oceania	Cook Islands	08 Sep 87	0	WPRO Memo, 8.9.87
Americas	Costa Rica	30 Jun 87	31	AMRO, 18.9.87
Africa	Cote d'Ivoire	13 Nov 86	118	AIDS Conf Brazzaville, 13.11.86
Americas	Cuba	09 Sep 87	5	Ministry of Health, 9.9.87
Asia	Cyprus	01 Jun 87	3	Ministry of Health, June 1987
Europe	Czechoslovakia	31 Mar 87	7	WHO Coll Ctr AIDS, Paris, 25.5.87
Europe	Denmark	30 Jun 87	176	WHO Coll Ctr AIDS, Paris, 1.9.87
Africa	Djibouti	01 Oct 87	0	EMRO Memo, 1.10.87
Americas	Dominica	30 Jun 87	5	CAREC Report, 17.9.87
Americas	Dominican Republic	31 Mar 87	200	AMRO, 1.6.87
Asia	Eastern Med Region	10 Sep 87	36	EMRO Memo, 10.9.87
Americas	Ecuador	15 Sep 87	52	AMRO, 18.9.87
Africa	Egypt	06 Jul 87	1	Ministry of Health, 6.7.87
Americas	El Salvador	30 Jun 87	12	AMRO, 18.9.87
Africa	Ethiopia	30 Jun 87	5	Surveillance & Epid Srvs, 2.7.87
Europe	Federal Republic Germany	30 Sep 87	1,400	FRG Working Group, AIDS, 30.9.87
Oceania	Fiji	08 Sep 87	0	WPRO Memo, 8.9.87
Europe	Finland	30 Jun 87	19	WHO Coll Ctr AIDS, Paris, 1.9.87
Europe	France	30 Jun 87	1,980	WHO Coll Ctr AIDS, Paris, 1.9.87
Americas	French Guiana	31 Dec 86	58	AMRO, 1.6.87
Oceania	French Polynesia	08 Sep 87	1	WPRO Memo, 8.9.87
Africa	Gabon	06 Jul 87	13	National AIDS Committee, 6.7.87

*Updated information.

Continued on next page

Continued from previous page

Cases of the Acquired Immunodeficiency Syndrome Reported to World Health Organization as of 21 Oct 87

Continent	Country or Territory	Date of Report	Number of Cases	Source
Africa	Gambia	16 Mar 87	14	Ministry of Health, WR telex, 16.3.87
Europe	German Democratic Republic	30 Jun 87	4	WHO Coll Ctr AIDS, Paris 1.9.87
Africa	Ghana	25 May 87	145	Ghana Perm Mission, Geneva, 25.5.87
Europe	Greece	30 Jun 87	49	WHO Coll Ctr AIDS, Paris, 1.9.87
Americas	Grenada	30 Jun 87	5	CAREC Surv Report, 87/7
Americas	Guadeloupe	31 Dec 86	40	WER No. 16, 17.4.87
Americas	Guatemala	30 Jun 87	27	AMRO, 18.9.87
Africa	Guinea	30 Jun 87	9	AFRO Memo, 7.7.87
Africa	Guinea-Bissau	30 Jun 87	2	AFRO Memo, 10.7.87
Americas	Guyana	31 Mar 87	1	CAREC Report, 17.9.87
Americas	Haiti	18 Sep 87	912	AMRO, 18.9.87
Americas	Honduras	30 Jun 87	29	AMRO, 18.9.87
Asia	Hong Kong	08 Sep 87	4	WPRO Memo, 8.9.87
Europe	Hungary	30 Jun 87	5	WHO Coll Ctr AIDS, Paris, 1.9.87
Europe	Iceland	30 Jun 87	4	WHO Coll Ctr AIDS, Paris, 1.9.87
Asia	India	09 May 87	9	Dr Dhanoa, Ministry of Health at WHA, 9.5.87
Asia	Indonesia	21 Apr 87	1	Natl Health Inst, 21.4.87
Europe	Ireland	30 Jun 87	19	WHO Coll Ctr AIDS, Paris, 1.9.87
Asia	Israel	30 Sep 87	42	Ministry of Health, September 1987
Europe	Italy	30 Aug 87	1,025	Bol Epidem Nazionale, 87/9
Americas	Jamaica	30 Jun 87	19	CAREC Report, 17.9.87
Asia	Japan	06 Oct 87	50	Ministry of Health, 6.10.87*
Africa	Kenya	30 Jul 87	625	Ministry of Health, 31.7.87
Asia	Korea, DPR	09 May 87	0	Mr Kum, Ministry of Health at WHA, 9.4.87
Asia	Korea, Rep	08 Sep 87	1	WPRO Memo, 8.9.87
Asia	Lebanon	03 Jun 87	3	EMRO fax., 21.6.87
Africa	Lesotho	13 Nov 86	1	AIDS Conf Brazzaville, 13.11.86
Africa	Liberia	12 Jun 87	2	Ministry of Health via AFRO Memo, 10.7.87
Europe	Luxembourg	31 Mar 87	7	WHO Coll Ctr AIDS, Paris, 1.9.87
Africa	Madagascar	25 Apr 87	0	AFRO Memo, 10.5.87
Africa	Malawi	13 Nov 86	13	AIDS Conf Brazzaville, 13.11.86
Asia	Malaysia	08 Sep 87	1	WPRO Memo, 8.9.87
Asia	Maldives	30 Jun 87	0	Ministry of Health, 30.6.87
Africa	Mali	08 Sep 87	0	Ministry of Health, 8.9.87
Europe	Malta	30 Jun 87	6	WHO Coll Ctr AIDS, Paris, 1.9.87
Oceania	Mariana Islands	05 Aug 87	0	Public Hlth Environm Servcs, 5.8.87
Americas	Martinique	31 Mar 87	25	CAREC Surv. Report, 87/7
Africa	Mauritania	13 Nov 86	0	AIDS Conf Brazzaville, 13.11.86
Africa	Mauritius	15 Sep 87	1	WR, Mauritius, 15.9.87
Americas	Mexico	30 Jun 87	534	AMRO, 18.9.87
Americas	Montserrat	31 Jul 87	0	CAREC Report, 17.9.87
Africa	Mozambique	30 Jun 87	1	Ministry of Health, 14.7.87
Asia	Nepal	09 May 87	0	Dr Baral, Ministry of Health at WHA, 9.5.87
Europe	Netherlands	30 Jun 87	308	WHO Coll Ctr AIDS, Paris, 1.9.87
Oceania	New Caledonia	08 Sep 87	0	WPRO Memo, 8.9.87
Oceania	New Zealand	30 Sep 87	54	Department of Health, 7.10.87*
Americas	Nicaragua	18 Sep 87	19	AMRO, 18.9.87
Africa	Nigeria	22 May 87	5	National AIDS Committee, 22.5.87
Europe	Norway	30 Jun 87	49	WHO Coll Ctr AIDS, Paris, 1.9.87
Americas	Panama	18 Sep 87	22	AMRO, 18.9.87
Oceania	Papua New Guinea	08 Sep 87	0	WPRO Memo, 8.9.87
Americas	Paraguay	30 Jun 87	14	AMRO, 18.9.87
Americas	Peru	15 Sep 87	44	AMRO, 18.9.87
Asia	Philippines	08 Sep 87	7	WPRO Memo, 8.9.87
Europe	Poland	30 Jun 87	2	WHO Coll Ctr AIDS, Paris, 1.9.87
Europe	Portugal	30 Jun 87	67	WHO Coll Ctr AIDS, Paris, 1.9.87
Asia	Qatar	09 May 87	9	Dr Al-Jaber, Ministry of Health at WHA, 9.5.87
Africa	Reunion	10 Jun 87	1	Dept Affaires Sanit & Soc, 23.6.87
Europe	Romania	31 Mar 87	2	WHO Coll Ctr AIDS, Paris, 1.9.87
Africa	Rwanda	30 Nov 86	705	Ministry of Health via AFRO Memo, 11.3.87

*Updated information.

Continued on next page

Continued from previous page

Cases of the Acquired Immunodeficiency Syndrome Reported to World Health Organization as of 21 Oct 87

Continent	*Country or Territory*	*Date of Report*	*Number of Cases*	*Source*
Oceania	Samoa	08 Sep 87	0	WPRO Memo, 8.9.87
Africa	Sao Tome/Principe	01 Dec 86	0	AFRO Memo, 21.4.87
Africa	Senegal	13 Nov 86	0	AIDS Conf Brazzaville, 13.11.86
Africa	Seychelles	13 Nov 86	0	AIDS Conf Brazzaville, 13.11.86
Asia	Singapore	30 Jun 87	2	Ministry of Health, 13.7.87
Oceania	Solomon Islands	08 Sep 87	0	WPRO Memo, 8.9.87
Africa	South Africa	11 Sep 87	81	Advisory Group on AIDS, 11.9.87*
Europe	Spain	30 Jun 87	508	WHO Coll Ctr AIDS, Paris, 1.9.87
Asia	Sri Lanka	14 Apr 87	2	SEARO, 14.4.87
Americas	St Christopher	31 Dec 86	1	AMRO, 1.6.87
Americas	St Lucia	31 Dec 86	3	AMRO, 1.6.87
Americas	St Vincent	31 Dec 86	3	AMRO, 1.6.87
Africa	Sudan	23 Aug 87	12	EMRO Memo, 23.8.87
Americas	Suriname	31 Mar 87	5	CAREC Report, 17.9.87
Africa	Swaziland	01 Jul 87	7	Ministry of Health via AFRO, 1.7.87
Europe	Sweden	18 Sep 87	139	EPID Aktuellt, SBL, 87/39
Europe	Switzerland	30 Jun 87	266	Bull Off Fed Sante Publ, 87/30
Africa	Tanzania	18 Apr 87	1,130	Dr Maselle, Geneva Mtg, 27.4.87
Asia	Thailand	30 Jun 87	11	Venereal Disease Division, July 1987
Africa	Togo	13 Nov 86	0	AIDS Conf Brazzaville, 13.11.86
Oceania	Tonga	06 Oct 87	1	AIDS Conf, Tokyo, 6.10.87*
Americas	Trinidad & Tobago	30 Jun 87	178	CAREC Report, 17.9.87
Africa	Tunisia	14 May 86	2	Ministry of Health at WHA, 14.5.86†
Asia	Turkey	30 Jun 87	21	Perm Mission Turkey, Geneva, 24.7.87
Americas	Turks & Caicos	30 Jun 87	4	CAREC Report, 17.9.87
Oceania	Tuvalu	08 Sep 87	0	WPRO Memo, 8.9.87
Africa	Uganda	28 Feb 87	1,138	Dr Okware, Geneva Mtg, 27.4.87
Europe	United Kingdom	30 Sep 87	1,067	CDR 87/39, 2.10.87
Americas	United States	28 Sep 87	42,354	AIDS Weekly Surv Rpt, 28.9.87
Americas	Uruguay	30 Jun 87	13	AMRO, 18.9.87
Europe	USSR	05 Aug 87	4	Ministry of Health, 5.8.87
Oceania	Vanuatu	08 Sep 87	0	WPRO Memo, 8.9.87
Americas	Venezuela	18 Sep 87	101	AMRO, 18.9.87
Asia	Viet Nam	08 Sep 87	0	WPRO Memo, 8.9.87
Europe	Yugoslavia	30 Jun 87	11	WHO Coll Ctr AIDS, Paris, 1.9.87
Africa	Zaire	30 Jun 87	335	Dept de Sante Publique, 6.8.87
Africa	Zambia	30 Jun 87	395	Ministry of Health, 27.7.87
Africa	Zimbabwe	28 Aug 87	380	Ministry of Health, 28.8.87
		Total	62,445	

*Updated information.
†Imported case.

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CONSULTANTS FOR **The Western Journal of Medicine** IN 1987

The editors wish to acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given by the following persons to the journal during the past year.

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Goldman, Lynn
Goldman, Richard
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Hollander, Harry
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Margaretten, William
Margolin, Fred
Margulis, Alexander R.
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Marr, J. Joseph
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Marshall, Randy
Matychowiak, Francis A.
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Mendelson, Terrie
Mertz, Gregory J.
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Miller, A. B.
Molutsky, Arno
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Morris, Cynthia D.
Morrison, Douglass A.
Mortensen, Mary Lund
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Mullins, William
Mustacchi, Piero O.

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Ramsey, Paul G.
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Rech, Stuart
Recker, Robert R.
Reddy, A. N.
Regelman, Warren
Reingold, Arthur
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Reynolds, Telfer B.
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Ries, Andrew L.
Ries, Curt A.
Risse, Guenter B.
Robertson, Gary L.
Robinson, Bruce E.
Rodnick, Jonathan E.
Rodriguez, Eloy
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Rosenberg, Philip
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Sack, Kenneth E.
Sacks, Susan T.
Saks, Bernie J.
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Schroeder, Steven A.
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Scott, Susan M.
Seaman, William E.
Selzer, Arthur
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Simon, Toby L.
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Tureen, Jay H.
Turnbull, Timothy L.
Tzamaloukas, Antonios H.

Van Brunt, Edmund E.
Van Epps, Dennis E.
Veasy, L. George
Verghese, Abraham
Vierling, John M.
Vyas, Girish N.

Wall, Susan D.
Wallerstein, Ralph O., Jr
Walsh, Thomas J.
Warnock, David
Watanakunakorn, Chatrchai
Watson, Robert D.
Weinstein, Philip R.
Welby, Dorothy
West, Sheila K.
Wheat, Lawrence J.
Wheeler, Henry O.
Wiedermann, Bernhard L.
Willett, Walter C.
Williams, Vernon R.
Wilner, Amy
Winkelstein, Warren
Wolfe, Elliott
Woolf, Paul D.
Wuepper, Kirk D.
Wynder, E. L.

Yelin, Edward
Yonekura, Margaret Lynn
Young, Lowell

Zabriskie, John B.
Zager, Philip G.
Ziegler, John
Zins, G. Brian
Zorgniotti, Adrian W.

AUTHOR INDEX

Aikawa, Jerry K., Denver . . . . . (Jul) 86
Ainsworth, Ronald E., Paradise, Calif . . . . . (Nov) 599
Akin, Barbara V., Orange, Calif . . . . . (Sep) 287
Alessi, David M., Los Angeles . . . . . (Oct) 475
Ampel, Neil M., Tucson . . . . . (Sep) 309
Antonovic, Ruza, Portland . . . . . (Sep) 333
Arevalo, Jose A., Sacramento, Calif . . . . . (Jul) 44
Arlington, Amber, Long Beach, Calif . . . . . (Oct) 474

Bailie, Ira E., Turlock, Calif . . . . . (Oct) 475
Bark, C. Jack, San Diego . . . . . (Sep) 340
Barnes, Allan M., Fort Collins, Colo . . . . . (Nov) 554
Barnett, Jeffrey B., Victoria, BC . . . . . (Oct) 474
Barnhart, Scott, Seattle . . . . . (Jul) 37
Basaca-Sevilla, Virginia, Manila, Philippines . . . . . (Dec) 723
Bayer, William H., Boise, Idaho . . . . . (Oct) 466
Becker, Thomas M., Albuquerque . . . . . (Nov) 554
Berke, Gerald, Los Angeles . . . . . (Oct) 475
Bernstein, Gerald S., Los Angeles . . . . . (Nov) 600
Blossom, John, Fresno, Calif . . . . . (Nov) 601
Book, Steven A., Berkeley, Calif . . . . . (Nov) 615
Boushey, Homer A., San Francisco . . . . . (Sep) 314
Braunstein, H., San Bernardino, Calif . . . . . (Nov) 600
Brigden, Malcolm L., Victoria, BC . . . . . (Oct) 474
Brillman, Judith, Stanford, Calif . . . . . (Oct) 469
Brody, Barbara L., La Jolla, Calif . . . . . (Sep) 350
Brook, Robert H., Santa Monica, Calif . . . . . (Nov) 609
Brown, David L., Houston . . . . . (Jul) 84
Buckberg, Gerald D., Los Angeles . . . . . (Jul) 54

Caldwell, John W., Bakersfield, Calif . . . . . (Nov) 593
Campbell, Stephen M., Portland . . . . . (Sep) 342
Caplin, Irvin, Palm Springs, Calif . . . . . (Aug) 205
Chassin, Mark R., Santa Monica, Calif . . . . . (Nov) 609
Cherubin, Charles E., Staten Island, NY . . . . . (Sep) 330
Chow, Anthony W., Vancouver . . . . . (Nov) 599
Colebunders, Robert, Kinshasa, Zaire . . . . . (Dec) 709
Collette, Linda, Salt Lake City . . . . . (Jul) 92
Collins, Kathryn Maino, Stockton, Calif . . . . . (Nov) 602
Cook, David M., Portland . . . . . (Aug) 161
Cope, Dennis W., Los Angeles . . . . . (Jul) 99
Corporon, Miguel Berry, Seattle . . . . . (Jul) 44
Csongradi, Carolyn, Hillsborough, Calif . . . . . (Nov) 601
Culler, Floyd L., La Jolla, Calif . . . . . (Nov) 591
Cunningham, George C., Berkeley, Calif . . . . . (Jul) 87

Dayrit, Manuel M., Manila, Philippines . . . . . (Dec) 723
de Andrés, R., Madrid . . . . . (Dec) 702
de Haas, David D., Bakersfield, Calif . . . . . (Nov) 593
Deiss, Andrew, Salt Lake City . . . . . (Aug) 196
Dembitsky, Walter P., San Diego . . . . . (Aug) 206
Devor, Daniel, Anaheim, Calif . . . . . (Oct) 432
Don, Burl R., San Francisco . . . . . (Oct) 449

Echenberg, Dean F., San Francisco . . . . . (Jul) 104
Ellis, Leland R., Bellevue, Wash . . . . . (Sep) 296
Embury, Stephen H., San Francisco . . . . . (Nov) 580
Eng, Robert H. K., East Orange, NJ . . . . . (Sep) 330
Epstein, David M., Berkeley, Calif . . . . . (Jul) 95

Felton, Jean Spencer, Irvine, Calif . . . . . (Jul) 40
Fink, Arlene, Santa Monica, Calif . . . . . (Nov) 609
Fleischer, Alan S., Tucson . . . . . (Oct) 428
Flink, Edmund B., Morgantown, WVa . . . . . (Jul) 86
Foulke, Garrett E., Sacramento, Calif . . . . . (Nov) 602
Fox, E. R. W., Coeur d'Alene, Idaho . . . . . (Aug) 225
Fredson, Deloris, Modesto, Calif . . . . . (Jul) 95
Freeman, Howard E., Los Angeles . . . . . (Aug) 165
Friedenberg, David S., San Francisco . . . . . (Aug) 214
Frohman, Elliot M., Irvine, Calif . . . . . (Oct) 486
Frontiera, Michael, Denver . . . . . (Aug) 157
Frye, Elizabeth, Orange, Calif . . . . . (Sep) 287

Gadek, James E., Columbus, Ohio . . . . . (Jul) 79
Gandour, Regina F., Sacramento, Calif . . . . . (Sep) 340
Ganelin, Robert S., Doha, Qatar . . . . . (Nov) 591
Geyer, Stanley J., Seattle . . . . . (Nov) 596
Glasgow, Marian, Boston . . . . . (Aug) 194
Goldman, Lynn R., Berkeley, Calif . . . . . (Jul) 95
Goodenough, Gerald K., Salt Lake City . . . . . (Jul) 92
Gordon, Geoffrey H., Portland . . . . . (Jul) 88
Gorlick, Gary, Los Angeles . . . . . (Sep) 340
Green, James R., San Francisco . . . . . (Jul) 104
Green, Lawrence W., Houston . . . . . (Sep) 346
Greenspoon, Jeffrey S., Los Angeles . . . . . (Nov) 600
Greer, Monte A., Portland . . . . . (Aug) 161
Grey, Todd C., Salt Lake City . . . . . (Aug) 207
Grossman, Moses, San Francisco . . . . . (Jul) 104
Guthkelch, A. Norman, Tucson . . . . . (Oct) 428

Haber, Judy, Fresno, Calif . . . . . (Nov) 558
Harris, Dona L., Salt Lake City . . . . . (Jul) 92
Havlir, Diane, San Francisco . . . . . (Jul) 65
Hay, William W., Jr, Denver . . . . . (Oct) 435
Hayes, Curtis G., Manila, Philippines . . . . . (Dec) 723
Hennrikus, Eileen F., San Ysidro, Calif . . . . . (Aug) 201
Herrera, M. I., Madrid . . . . . (Dec) 702
Hessel, Samuel J., Scottsdale, Ariz . . . . . (Sep) 357
Horowitz, R. E., Burbank, Calif . . . . . (Nov) 600
Howard, Matthew L., Ukiah, Calif . . . . . (Aug) 208
Huante, David, Seattle . . . . . (Jul) 44
Hubbell, F. Allan, Orange, Calif . . . . . (Sep) 287

Ito, M., Tokyo . . . . . (Dec) 719

Jackson, Richard J., Berkeley, Calif . . . . . (Jul) 95, (Nov) 615
James, D. Geraint, London . . . . . (Aug) 193
Jaski, Brian E., San Diego . . . . . (Aug) 206
Jennings, Robert B., Durham, NC . . . . . (Jul) 62
Jewesson, Peter J., Vancouver . . . . . (Nov) 599
Johnson, Alexander C., Great Falls, Mont . . . . . (Aug) 207
Johnson, William W., Monte Sereno, Calif . . . . . (Sep) 339
Jones, Kenneth L., La Jolla, Calif . . . . . (Nov) 591
Jung, Ralph C., Los Angeles . . . . . (Aug) 205

Kan, Yuet W., San Francisco . . . . . (Oct) 462
Katz, Edward R., Scottsdale, Ariz . . . . . (Sep) 357
Kawaguchi, Y., Geneva . . . . . (Dec) 719
Kelly, Kem, Modesto, Calif . . . . . (Jul) 95
Kennaugh, Jan M., Denver . . . . . (Oct) 435
Kleinman, Steven H., Los Angeles . . . . . (Jul) 86
Knoepfler, Gayle Stewart, Bellevue, Wash . . . . . (Sep) 296
Knoepfler, Peter, Bellevue, Wash . . . . . (Sep) 296
Kosecoff, Jacqueline, Santa Monica, Calif . . . . . (Nov) 609
Kramer-Levien, Denise J., Bellevue, Wash . . . . . (Sep) 296
Kraus, Jess F., Los Angeles . . . . . (Aug) 208

Labadie, Enrique L., Tucson . . . . . (Sep) 309
Lalouel, Jean-Marc, Salt Lake City . . . . . (Oct) 423
Langer, Glenn A., Los Angeles . . . . . (Jul) 54
Larios, Miriam, Stanford, Calif . . . . . (Jul) 44
Lathrop, G. Mark, Salt Lake City . . . . . (Oct) 423
Lee, David B. N., Los Angeles . . . . . (Nov) 569
Leonhardt, Fred, Portland . . . . . (Oct) 481
Leppert, Mark F., Salt Lake City . . . . . (Oct) 423
Levy, David E., New York . . . . . (Aug) 191
Levy, Jonathan M., Scottsdale, Ariz . . . . . (Sep) 357
Lewis, Charles E., Los Angeles . . . . . (Aug) 165
Linn, Lawrence S., Los Angeles . . . . . (Jul) 99
Lohiya, Ghanshyam, Costa Mesa, Calif . . . . . (Sep) 341
Longstreth, W. T., Jr, Seattle . . . . . (Aug) 193
Lubick, Harold A., Los Angeles . . . . . (Jul) 86
Lyden, Patrick D., San Diego . . . . . (Aug) 198

McCarty, James B., Fresno, Calif . . . . . (Nov) 558
Malish, David M., San Jose, Calif . . . . . (Aug) 205
Mann, Bruce A., Albuquerque . . . . . (Aug) 200
Mann, Jonathan M., Geneva . . . . . (Nov) 554, (Dec) 693, 694, 731
Marshall, Lawrence F., San Diego . . . . . (Nov) 598
Martin, Joseph B., Boston . . . . . (Oct) 486
Martin, Richard J., Denver . . . . . (Jul) 41
Massell, Theodore B., Los Angeles . . . . . (Oct) 475
Mengle, Donald, Berkeley, Calif . . . . . (Jul) 95
Meyer, Anthony J., Geneva . . . . . (Dec) 716
Moatamed, Farhad, Salt Lake City . . . . . (Aug) 196
Monzon, Ofelia T., Manila, Philippines . . . . . (Dec) 723
Moorhead, George V., Sacramento, Calif . . . . . (Nov) 602
Morris, R. Curtis, Jr., San Francisco . . . . . (Nov) 577
Morriss, Frank H., Jr, Iowa City . . . . . (Oct) 463
Mulholland, Michael W., Seattle . . . . . (Sep) 301
Murdock, Richard T., Salt Lake City . . . . . (Oct) 467
Musher, Daniel M., Houston . . . . . (Jul) 84
Myers, Adam M., Denver . . . . . (Aug) 157

Nájera, Rafael, Madrid . . . (Dec) 702
Nakamura, Yusuke, Salt Lake City . . . (Oct) 423
Nathan, Peter A., Portland . . . (Nov) 598
Nava, Adolph J., Bakersfield, Calif . . . (Nov) 593
Neinstein, Lawrence S., Los Angeles . . . (Aug) 218
Nellans, Roger E., Bellevue, Wash . . . (Sep) 296
Nelson, Tony A., Los Angeles . . . (Nov) 549
Nichols, Joni, San Francisco . . . (Sep) 314

O'Connell, Peter, Salt Lake City . . . (Oct) 423
Okware, Samuel Ikwaras, Entebbe, Uganda . . . (Dec) 726
Oliva, Geraldine E., San Francisco . . . (Jul) 104
O'Malley, Robert J., Sacramento, Calif . . . (Oct) 487
Ortiz, Maria Teresa, San Francisco . . . (Jul) 44

Paige, Carol, Portland . . . (Sep) 333
Passaro, Edward, Jr, Los Angeles . . . (Sep) 329
Paxton, H., Portland . . . (Aug) 161
Peck, Michael D., Tucson . . . (Jul) 81
Pedersen, Donald M., Salt Lake City . . . (Oct) 467
Pederson, Leigh, San Diego . . . (Aug) 201
Phillipson, Eliot A., Toronto, Ontario . . . (Nov) 588
Pilcher, Charles A., Woodinville, Wash . . . (Sep) 339
Pinson, C. Wright, Portland . . . (Sep) 333
Piot, Peter, Antwerp, Belgium . . . (Dec) 709
Poland, Jack D., Fort Collins, Colo . . . (Nov) 554
Pompidou, Alain, Paris . . . (Dec) 730
Pretorius, Harold T., San Diego . . . (Sep) 292

Quan, Thomas J., Fort Collins, Colo . . . (Nov) 554
Quenzer, Ronald W., Albuquerque . . . (Aug) 200

Ranney, Helen M., La Jolla, Calif . . . (Sep) 340
Resendes, Mariela, San Francisco . . . (Jul) 48
Rhee, Kenneth J., Sacramento, Calif . . . (Oct) 487
Ries, Kristen, Salt Lake City . . . (Oct) 467
Ries, Richard, Seattle . . . (Jul) 86
Rimkus, Daniel S., San Diego . . . (Sep) 292
Riner, R. Myles, Modesto, Calif . . . (Nov) 602
Robbins, Alan, Sepulveda, Calif . . . (Jul) 99
Robbins, Dick L., Sacramento, Calif . . . (Aug) 210
Roberts, James C., Jr, Torrance, Calif . . . (Aug) 206
Robles, Antonio, Loma Linda, Calif . . . (Oct) 432
Rodman, David M., Denver . . . (Jul) 41
Rogers, Martha F., Atlanta . . . (Jul) 109
Rosenstock, Linda, Seattle . . . (Jul) 37
Rubin, Edward M., San Francisco . . . (Oct) 462
Rucker, Lloyd, Orange, Calif . . . (Sep) 287
Rude, Robert K., Los Angeles . . . (Nov) 549
Russell, Hanafi, Berkeley, Calif . . . (Nov) 615
Rutherford, George W., San Francisco . . . (Jul) 104
Ryzen, Elisabeth, Los Angeles . . . (Nov) 549

Sabatier, Renée C., London . . . (Dec) 713
Sarsfield, Edwin S., San Francisco . . . (Jul) 104
Schaeffer, L. Daniel, Los Angeles . . . (Jul) 86
Schambelan, Morris, San Francisco . . . (Oct) 449
Schmerl, E. Fritz, Hayward, Calif . . . (Oct) 475
Schmidt-Nowara, Wolfgang W., Albuquerque . . . (Nov) 561
Schneiderman, Henry, Farmington, Conn . . . (Nov) 623
Schueler, Mark S., Grand Rapids, Mich . . . (Jul) 92
Sharma, Om P., Los Angeles . . . (Aug) 168
Shaw, Nancy S., San Francisco . . . (Jul) 104
Sherman, Ronald A., Sacramento, Calif . . . (Sep) 340
Simon, Harold J., La Jolla, Calif . . . (Sep) 350
Small, James M., Salt Lake City . . . (Aug) 196
Smallwood, Dennis E., La Jolla, Calif . . . (Sep) 350
Smith, David L., Portland . . . (Sep) 342
Solomon, David H., Los Angeles . . . (Nov) 609
Spath, David P., Berkeley, Calif . . . (Nov) 615
Spiegel, James, Sacramento, Calif . . . (Sep) 340
Spiegel, Renee A., Scottsdale, Ariz . . . (Sep) 357
Strausbaugh, Larry J., Portland . . . (Sep) 333
Stroud, Florence, San Francisco . . . (Jul) 104
Swedberg, Jay, Casper, Wyo . . . (Sep) 335
Sweeney, E. S., Salt Lake City . . . (Aug) 207

Taffet, George E., Houston . . . (Jul) 84
Tamashiro, Hiko, Geneva . . . (Dec) 719
Teret, Stephen P., Baltimore, MD . . . (Aug) 208
Terry, Phillip, Sacramento, Calif . . . (Nov) 602
Tierney, Lawrence M., Jr, San Francisco . . . (Jul) 65
Tillisch, Jan H., Los Angeles . . . (Jul) 54
Trujillo-Juarez, Daniel, La Jolla, Calif . . . (Nov) 591
Tunzi, Marc, Crow Agency, Mont . . . (Sep) 339
Turner, James E., Sacramento, Calif . . . (Oct) 487

Van Gundy, Karl, Los Angeles . . . (Aug) 168
Vasquez, Tony E., San Diego . . . (Sep) 292
Villar, Hugo V., Tucson . . . (Jul) 81
von Reyn, C. Fordham, Geneva . . . (Dec) 694

Wacker, Warren E. C., Cambridge, Mass . . . (Jul) 86
Wang, Hansen, Fontana, Calif . . . (Oct) 432
Wara, Diane W., San Francisco . . . (Jul) 104
Ward, Darrell E., Portland . . . (Oct) 481
Ward, Richard E., Sacramento, Calif . . . (Oct) 487
Warren, Charles, Fontana, Calif . . . (Oct) 432
Watts, Malcolm S. M., San Francisco . . . (Jul) 79, 80 (Aug) 191, 195, (Sep) 329, 331, (Oct) 462, (Nov) 588, 590, (Dec) 692
Weinstein, Daniel H., San Francisco . . . (Jul) 104
Wendel, Thomas H., Casper, Wyo . . . (Sep) 335
Werdegar, David, San Francisco . . . (Jul) 104
Whang, Robert, Oklahoma City . . . (Jul) 86
Wheat, Mary E., Bronx, NY . . . (Oct) 477
White, George L., Salt Lake City . . . (Oct) 467
White, Mark E., Fort Collins, Colo . . . (Nov) 554
White, Raymond L., Salt Lake City . . . (Oct) 423
White, Richard H., Sacramento, Calif . . . (Aug) 210
Wiggins, Robert V., Albuquerque . . . (Nov) 561
Willits, Neil H., Sacramento, Calif . . . (Oct) 487
Wilson, Dana E., Salt Lake City . . . (Aug) 196
Wintemute, Garen J., Sacramento, Calif . . . (Aug) 208
Wishart, David L., Yakima, Wash . . . (Aug) 207
Wofsy, Constance B., San Francisco . . . (Jul) 104
Wofsy, David, San Francisco . . . (Aug) 181
Wollitzer, Alison Okada, San Francisco . . . (Jul) 44
Wood, Stephen D., Salt Lake City . . . (Oct) 467

Yu, George C., Los Angeles . . . (Nov) 569

Zelicoff, Alan P., Albuquerque . . . (Nov) 598

IN MEMORIAM

Arizona Medical Association:

Atonna, Guy B., Sep 15, 1987 . . . (Dec) 676
Cackler, C. Stephen, Aug 2, 1987 . . . (Dec) 676
Cruthirds, Archie E., Sep 7, 1987 . . . (Dec) 676

California Medical Association:

Armstrong, Elwin L., Sep 1, 1987 . . . (Dec) 676
Avon, Henry A., Aug 27, 1987 . . . (Dec) 676
Barnes, James P., May 21, 1987 . . . (Aug) 140
Bazilauskas, V. Faustin, Jun 20, 1987 . . . (Oct) 420
Bean, Joseph Patrick, Jun 24, 1987 . . . (Oct) 420
Becker, Sidney F., Sep 8, 1987 . . . (Dec) 676
Boros, Harold H., Sep 8, 1987 . . . (Dec) 676
Bosworth, David B., Jul 12, 1987 . . . (Nov) 542
Brady, James F., Sep 9, 1987 . . . (Dec) 676
Canelo, C. Kelly, Jun 13, 1987 . . . (Oct) 420
Cardey, Norman L., Apr 17, 1987 . . . (Aug) 140
Carmack, James C., Apr 12, 1987 . . . (Aug) 140
Cella, Robert L., Aug 28, 1987 . . . (Dec) 676
Cerv, Ernest A., May 1987 . . . (Aug) 140
Chamberlain, Calvin B., Sep 15, 1987 . . . (Dec) 676
Chatterjee, Alo, Apr 26, 1987 . . . (Aug) 140
Chatterjee, Chitta R., Apr 26, 1987 . . . (Aug) 140
Coy, L. Pierce, May 30, 1987 . . . (Aug) 140
Crane, Jay J., Jun 25, 1987 . . . (Oct) 420
Cray, G. Cameron, Apr 27, 1987 . . . (Aug) 140
Cunningham, Bernard P., Jun 1987 . . . (Oct) 420
Davis, Stella, Aug 1, 1987 . . . (Dec) 676
Dunbar, William H. IV, May 20, 1987 . . . (Oct) 420
Dunievitz, Max, Jun 19, 1987 . . . (Oct) 420
Engstrom, Robert E., Apr 9, 1987 . . . (Aug) 140
Esslinger, Gillis A., Jul 16, 1987 . . . (Nov) 542
Franklin, Roland G., Apr 5, 1987 . . . (Aug) 140
Fry, Leonard C., Jul 18, 1987 . . . (Dec) 676
Gardiner, Frederick S., Feb 10, 1987 . . . (Aug) 140
Gonda, Thomas A., Aug 12, 1987 . . . (Nov) 542
Gucker, Thomas III, Mar 31, 1987 . . . (Aug) 140
Guida, Anthony J., Jul 5, 1987 . . . (Nov) 542
Hains, William L., May 29, 1987 . . . (Oct) 420
Hansen, Daniels D., Aug 26, 1987 . . . (Dec) 676
Hendricks, Max, Sep 10, 1987 . . . (Dec) 676
Hoiland, Dean, Oct 18, 1987 . . . (Dec) 676
Horton, Roger E., Apr 23, 1987 . . . (Oct) 420
Hoskins, H. Dean, Sep 17, 1987 . . . (Dec) 676

Jessup, Robert Bruce, Jun 2, 1987 . . . (Aug) 140
John, Edward A., Jul 13, 1987 . . . (Dec) 676
Kearney, Sanborn G., Apr 5, 1987 . . . (Aug) 140
Kenney, John Meredith, May 31, 1987 . . . (Oct) 420
Kern, Maximilian C., Aug 26, 1987 . . . (Dec) 676
Kimball, Theodore S., Apr 22, 1987 . . . (Oct) 420
Koenigsberger, Ernst, Apr 22, 1987 . . . (Aug) 140
Kuhn, Richard J., May 7, 1987 . . . (Oct) 420
Leland, John A. C., Jr, Jun 23, 1987 . . . (Oct) 420
Lewis, Jack J., Jun 15, 1987 . . . (Oct) 420
Lincoln, Charles S., Jr, May 29, 1987 . . . (Oct) 420
Loignon, Henri P., May 22, 1987 . . . (Aug) 140
Long, Albert E., Aug 31, 1987 . . . (Dec) 676
Long, James C., Aug 4, 1987 . . . (Dec) 676
Lopes, John D., May 23, 1987 . . . (Aug) 140
Lutz, Michael D., Mar 1987 . . . (Aug) 140
Lyons, Harold M., Sep 7, 1987 . . . (Dec) 676
McCrea, Francis R., Feb 27, 1987 . . . (Aug) 140
McGirr, John I., Sep 2, 1987 . . . (Dec) 676
McGuire, Frank A., Mar 3, 1987 . . . (Aug) 140
McNair, Joel N., Jul 27, 1987 . . . (Dec) 676
Macumber, Harold H., Sep 4, 1987 . . . (Dec) 676
Magit, Jack R., Apr 1, 1987 . . . (Oct) 420
Mahannah, L. Duke, Apr 21, 1987 . . . (Oct) 420
Maloney, Harold P., Jul 31, 1987 . . . (Dec) 676
Merkley, Ralph G., Aug 6, 1987 . . . (Nov) 542
Mintz, Samuel, Sep 8, 1987 . . . (Dec) 676
Moose, Ray M., Jul 14, 1987 . . . (Nov) 542
Munch, Paul F., Jun 3, 1987 . . . (Oct) 420
Nelson, Norman B., Jun 12, 1987 . . . (Oct) 420
Nordstrom, Ray C., Jul 3, 1987 . . . (Nov) 542
Norris, William J., Mar 27, 1987 . . . (Oct) 420
Nunn, Allan T., Jul 1, 1987 . . . (Nov) 542
Palmer, Bean Mark, Apr 10, 1987 . . . (Oct) 420
Powell, Tracy O., Feb 12, 1987 . . . (Oct) 420
Pritcher, J. L., Mar 17, 1987 . . . (Oct) 420
Purcell, Edward F., May 20, 1987 . . . (Oct) 420
Quirmbach, Robert P., Jul 17, 1987 . . . (Nov) 542
Ramirez, Xavier Hall, Jul 10, 1987 . . . (Nov) 542
Reid, Robert B., Jul 7, 1987 . . . (Dec) 676
Rhee, James L., Jul 28, 1987 . . . (Nov) 542
Rodnick, Norman L., Jun 14, 1987 . . . (Dec) 676
Sampson, Pearl M., Feb 2, 1987 . . . (Oct) 420
Schmidt, Hans, Mar 29, 1987 . . . (Oct) 420
Segar, Laurence F., May 6, 1987 . . . (Oct) 420
Shaw, Edward B., Sep 9, 1987 . . . (Dec) 676
Skillen, Jane, Jul 3, 1987 . . . (Dec) 676
Smith, Samuel Newlan, Aug 23, 1987 . . . (Dec) 676
Snook, Harold, Apr 23, 1987 . . . (Oct) 420
Sorenson, Lowell E., Jul 7, 1987 . . . (Oct) 420
Stengert, Krzysztof B., Aug 1987 . . . (Nov) 542
Sullivan, John Joseph, Apr 16, 1987 . . . (Oct) 420
Taube, Edward I., Apr 1, 1987 . . . (Oct) 420
Tucker, Wilson D., Aug 13, 1987 . . . (Nov) 542
Ulick, Herbert, Feb 7, 1987 . . . (Oct) 420
Van De Pol, Andrew, Aug 10, 1987 . . . (Nov) 542
Walters, Willard B., Apr 19, 1987 . . . (Oct) 420
Wick, Ward, Aug 22, 1987 . . . (Dec) 676
Williams, Malvin J., Jun 1987 . . . (Oct) 420
Wilson, William H., May 9, 1987 . . . (Nov) 542
Wimmer, Shirley Douglas, Aug 27, 1987 . . . (Dec) 676
Wing, Willard J., Aug 1987 . . . (Nov) 542
Wise, Edith P., Apr 2, 1987 . . . (Nov) 542
Wolfson, Mast, Apr 17, 1987 . . . (Nov) 542

Idaho Medical Association:
Crowe, Frank W., Apr 29, 1987 . . . (Nov) 542
Espeland, Duane H., Apr 7, 1987 . . . (Nov) 542
Worden, Donald K., Jul 21, 1987 . . . (Nov) 542

New Mexico Medical Society:
Alhadeff, Norman L., Jun 11, 1987 . . . (Aug) 140
Bivens, Melvin D., Jun 3, 1987 . . . (Aug) 140
Cianci, James G., Albuquerque . . . (Oct) 420
Draelos, Theodore T., Sep 14, 1987 . . . (Nov) 542
Mix, Nancy J., Jun 11, 1987 . . . (Aug) 140
Moore, John L., Jul 15, 1987 . . . (Oct) 420
Primer, Benjamin, Jr, Sep 6, 1987 . . . (Dec) 676
Ydens, Jan W., Aug 28, 1987 . . . (Nov) 542

Utah Medical Association:
Anderson, Grant Y., Jun 15, 1987 . . . (Dec) 676
Budge, Oliver W., May 19, 1987 . . . (Aug) 140
Graham, Oscar J., May 22, 1987 . . . (Dec) 676
Hashimoto, Edward Ichiro, Aug 23, 1987 . . . (Dec) 676
Poulsen, J. Robert, Sep 2, 1987 . . . (Dec) 676

SUBJECT INDEX

A

Acquired Immunodeficiency Syndrome, see *Peripheral Blood and Bone Marrow Abnormalities in the*
Actinomycosis, see *Disseminated*
Acute Symptoms in Persons Residing Near a Field Treated With the Soil Fumigants Methyl Bromide and Chloropicrin (Public Health), Lynn R. Goldman, Donald Mengle, David M. Epstein, Deloris Fredson, Kem Kelly, Richard J. Jackson . . . (Jul) 95
Adolescents, see *Preventive Care Screening*
Advances in the Prenatal Diagnosis of Sickle Cell Anemia (Medical Staff Conference), Discussant: Stephen H. Embury (Nov) 580

AIDS—A Global Perspective—Special Issue:
The Deadly Grip of AIDS, Malcolm S. M. Watts . . . (Dec) 692
AIDS—A Global Perspective, Jonathan M. Mann . . . (Dec) 693
Global Epidemiology, C. Fordham von Reyn, Jonathan M. Mann (Dec) 694
Human Immunodeficiency Virus and Related Retroviruses, Rafael Nájera, M. I. Herrera, R. de Andrés . . . (Dec) 702
Clinical Manifestations and the Natural History of HIV Infection in Adults, Peter Piot, Robert Colebunders . . . (Dec) 709
Social, Cultural and Demographic Aspects of AIDS, Renée C. Sabatier . . . (Dec) 713
A New World With AIDS—Health Promotion as a Catalyst for Change, Anthony J. Meyer . . . (Dec) 716
AIDS Prevention and Control in Japan, Hiko Tamashiro, Y. Kawaguchi, M. Ito . . . (Dec) 719
Emerging Patterns of HIV Infection and Control in the Philippines, Manuel M. Dayrit, Ofelia T. Monzon, Virginia Basaca-Sevilla, Curtis G. Hayes . . . (Dec) 723
Towards a National AIDS-Control Program in Uganda, Samuel Ikwaras Okware . . . (Dec) 726
The French National Program for the Prevention and Control of AIDS, Alain Pompidou . . . (Dec) 730
The World Health Organization's Global Strategy for the Prevention and Control of AIDS, Jonathan M. Mann . . . (Dec) 732

AIDS Prevention and Control in Japan (AIDS—A Global Perspective), Hiko Tamashiro, Y. Kawaguchi, M. Ito . . . (Dec) 719
Alpha-Fetoprotein Screening Program, see *California*
Amyloidosis, see *Biochemical and Clinical Aspects of*
Anosmia, see *Causes of*
Antinuclear Antibodies, see *Clinical Significance and Interpretation of*
α_1-Antitrypsin—An Investigative Odyssey From the Benchtop to the Bedside (Editorial), James E. Gadek . . . (Jul) 79
Apnea, see *Tracheostomy Tube Failure in Obstructive Sleep*
Are We a Violent Nation? (Editorial) . . . (Aug) 191
Are We Losing Ourselves Among the Trees? (Editorial) . . . (Jul) 80
Aspergillus Vertebral Osteomyelitis in Seemingly Immunocompetent Drug Addicts, see *Hematogenously Acquired*
Association of α_1-Antitrypsin Deficiency With Lung and Liver Diseases (Medical Progress), Mariela Resendes . . . (Jul) 48
Editorial, James E. Gadek . . . (Jul) 79
Asthma and Urticaria After Hepatitis A Vaccination (Correspondence), Ghanshyam Lohiya . . . (Sep) 341
Asthma Mortality (Medical Staff Conference), Discussants: Homer A. Boushey, Joni Nichols . . . (Sep) 314

B

Bacterial Infections of the Central Nervous System, see *Chemotherapy for*
Bacterial Meningitis in the 1980s, or One Drug or Many? (Editorial), Charles E. Cherubin, Robert H. K. Eng . . . (Sep) 330
Battlefield Called Sarcoidosis (Editorial), D. Geraint James . . . (Aug) 193

Biochemical and Clinical Aspects of Amyloidosis (Medical Staff Conference), Discussants: Diane Havlir, Lawrence M. Tierney, Jr . . . . . (Jul) 65
Blood and Bone Marrow Abnormalities in the Acquired Immunodeficiency Syndrome, see *Peripheral*
Blood Urea Nitrogen and Glucose Level Screening in Medical Admissions—Impact on Patient Management, see *Electrolyte*

Book Reviews:

Endourology, *Carson et al* . . . . . (Nov) 624
Trauma in Children, *Marcus* . . . . . (Nov) 568
Ultrastructural Appearances of Tumours—Diagnosis and Classification of Human Neoplasia by Electron Microscopy, *Henderson et al* (Nov) 622

Botulism, see *Wound*
Brain Death, see *Criteria for*
Brain Stem, see *Tuberculoma of the*

C

California Alpha-Fetoprotein Screening Program Defended (Correspondence), George C. Cunningham . . . . . ((Jul) 87
California Drinking Water, see *Chemical Contamination*
Cancer Patients, see *Pain Control in*
Candida glabrata, see *Catheter-Related Thrombophlebitis of the Superior Vena Cava Caused by*
Cardiac Arrest, see *Coma After*
Cardiac Arrest, see *Neurologic Sequelae of*
Cardiac Ischemia. Part II—Reperfusion and Treatment (Specialty Conference) . . . . . (Jul) 54
Editorial Comment, Robert B. Jennings . . . . . (Jul) 62
Cardiac Transplants, see *Medicare-Funded*
Carpal Tunnel Syndrome in Grocery Checkers—A Cluster of Work-Related Illness (Clinical Investigation), Scott Barnhart, Linda Rosenstock . . . . . (Jul) 37
Correspondence, Peter A. Nathan . . . . . (Nov) 598
Categorization of Hospital Emergency Services—Developing Valid Criteria (Health Care Delivery), R. Myles Riner, Kathryn Maino Collins, Garrett E. Foulke, George V. Moorhead, Phillip Terry . . . . . (Nov) 602
Cathartics in Overdose Management, see *Hypernatremia Associated With*
Catheter-Related Thrombophlebitis of the Superior Vena Cava Caused by *Candida glabrata*, Carol Paige, C. Wright Pinson, Ruza Antonovic, Larry J. Strausbaugh . . . . . (Sep) 333
Causes of Anosomia (Correspondence), Irvin Caplin . . . . . (Aug) 205
David M. Malish . . . . . (Aug) 205
Central Nervous System, see *Chemotherapy for Bacterial Infections of the*
Cerebral Metastases, see *Rhabdomyosarcoma of the Heart With*
Cervical Spine Injury, see *Patterns of*
Chemical Contamination of California Drinking Water (Public Health), Hanafi Russell, Richard J. Jackson, David P. Spath, Steven A. Book . . . . . (Nov) 615
Chemotherapy for Bacterial Infections of the Central Nervous System (Clinical Review), Neil M. Ampel, Enrique L. Labadie . . . . (Sep) 309
Editorial, Charles E. Cherubin, Robert H. K. Eng . . . . . (Sep) 330
Chief Complaint (Editorial) . . . . . (Sep) 331
Chloropicrin, see *Acute Symptoms in Persons Residing Near a Field Treated With the Soil Fumigants Methyl Bromide and*
Cholecystectomy Patients, see *Oral Cholecystography and Sonography of Gallbladder in*
Cholelithiasis—An Autopsy Study, see *Ethnic Variability in*
Clinical Disorders of Phosphorus Metabolism (Clinical Review), George C. Yu, David B. N. Lee . . . . . (Nov) 569

Clinical Investigation:

Carpal Tunnel Syndrome in Grocery Checkers—A Cluster of Work-Related Illness, Scott Barnhart, Linda Rosenstock . . . . (Jul) 37
Correspondence, Peter A. Nathan . . . . . (Nov) 598
Diagnostic Value of Thyrotropin-Releasing-Hormone Stimulation in Patients With Pituitary Tumor, David M. Cook, Monte A. Greer, H. Paxton . . . . . (Aug) 161
Peripheral Blood and Bone Marrow Abnormalities in the Acquired Immunodeficiency Syndrome, Michael Frontiera, Adam M. Myers . . . . . (Aug) 157
Electrolyte, Blood Urea Nitrogen and Glucose Level Screening in Medical Admissions—Impact on Patient Management, Lloyd Rucker, F. Allan Hubbell, Barbara V. Akin, Elizabeth Frye . . . . . (Sep) 287
Correspondence, R. E. Horowitz . . . . . (Nov) 600
H. Braunstein . . . . . (Nov) 600
Mapping Aproaches to Gene Identification in Humans, Raymond L. White, Jean-Marc Lalouel, G. Mark Lathrop, Mark F. Leppert, Yusuke Nakamura, Peter O'Connell . . . . . (Oct) 423
Editorial, Edward M. Rubin, Yuet W. Kan . . . . . (Oct) 462
Low Blood Mononuclear Cell Magnesium Content and Hypocalcemia in Normomagnesemic Patients, Elisabeth Ryzen, Tony A. Nelson, Robert K. Rude . . . . . (Nov) 549

Clinical Manifestations and the Natural History of HIV Infection in Adults, Peter Piot, Robert Colebunders (AIDS—A Global Perspective) . . . . . (Dec) 709

Clinical Review:

Chemotherapy for Bacterial Infections of the Central Nervous System, Neil M. Ampel, Enrique L. Labadie . . . . . (Sep) 309
Editorial, Charles E. Cherubin, Robert H. K. Eng . . . . . (Sep) 330
Clinical Disorders of Phosphorus Metabolism, George C. Yu, David B. N. Lee . . . . . (Nov) 569
Editorial Comment, R. Curtis Morris, Jr . . . . . (Nov) 577

Clinical Significance and Interpretation of Antinuclear Antibodies (Topics in Primary Care Medicine), Richard H. White, Dick L. Robbins . . . . . (Aug) 210
Colon, see *Perforated Diverticulitis of the Transverse*
Coma After Cardiac Arrest—How Much Care Is Enough? (Editorial), David E. Levy . . . . . (Aug) 191

Commentary:

Right Way to Go, E. R. W. Fox . . . . . (Aug) 225
Genetic Markers in Huntington's Disease, Elliot M. Frohman, Joseph B. Martin . . . . . (Oct) 486

Condom Use, Not Barrier Method, To Prevent Heterosexual HIV Infection (Correspondence), Jeffrey S. Greenspoon, Gerald S. Bernstein . . . . . (Nov) 600
Consent and Confidentiality Laws for Minors in the Western United States (Special Article), Lawrence S. Neinstein . . . . . (Aug) 218
Controlling Perinatally Acquired HIV Infection (Editorial Comment), Martha F. Rogers . . . . . (Jul) 109
Corporate Physician Today, Jean Spencer Felton . . . . . (Jul) 40

Correspondence:

Asthma and Urticaria After Hepatitis B Vaccination, Ghanshyam Lohiya . . . . . (Sep) 341
California Alpha-Fetoprotein Screening Program Defended, George C. Cunningham . . . . . (Jul) 87
Carpal Tunnel Syndrome, Peter A. Nathan . . . . . (Nov) 598
Causes of Anosmia, Irvin Caplin . . . . . (Aug) 205
David M. Malish . . . . . (Aug) 205
Condom Use, Not Barrier Method, To Prevent Heterosexual HIV Infection, Jeffrey S. Greenspoon, Gerald S. Bernstein . . . . . (Nov) 600
Criteria for Brain Death, Lawrence F. Marshall . . . . . (Nov) 598
Dental Professionals and HIV Infection, L. Daniel Schaeffer, Harold A. Lubick, Steven H. Kleinman . . . . . (Jul) 86
Fear of the Unknown, Ira E. Bailie . . . . . (Oct) 475
Heart Disease and Mortality, James C. Roberts, Jr . . . . . (Aug) 206
Hypomagnesemia, Edmund B. Flink, Jerry K. Aikawa, Robert Whang, Warren E. C. Wacker . . . . . (Jul) 86
Insects in the Operating Room, Ronald A. Sherman, James Spiegel, Regina F. Gandour . . . . . (Sep) 340
Medicare-Funded Cardiac Transplants, Brian E. Jaski, Sidney C. Smith, Walter P. Dembitsky . . . . . (Aug) 206
More Insects in the Operating Room, John Blossom . . . . . (Nov) 601
Opposing Views on Deaths From Firearms, Alexander C. Johnson . . . . . (Aug) 207
Matthew L. Howard . . . . . (Aug) 208
Reply, Garen J. Wintemute, Stephen P. Teret, Jess F. Kraus (Aug) 208
Overuse of Health Resources by Penicillin-Sensitive Children, Charles A. Pilcher . . . . . (Sep) 339
Pain Control in Cancer Patients, Amber Arlington . . . . . (Oct) 474
Reply, Malcolm L. Brigden, Jeffrey B. Barnett . . . . . (Oct) 474

Phosphorus and Water, Carolyn Csongradi . . . . . (Nov) 601
Physicians and the Death Penalty, Todd C. Grey, E. S. Sweeney (Aug) 207
David L. Wishart . . . . . (Aug) 207
Plight of Public Hospitals, Ralph C. Jung . . . . . (Aug) 205
Preventive Care Screening for Adolescents—What About Substance Abuse Screening?, Richard Ries . . . . . (Jul) 86
Primary Care—Does It Have a Future?, William W. Johnson . . . (Sep) 339
'Screening' and 'Routine' Testing, R. E. Horowitz . . . . . (Nov) 600
H. Braunstein . . . . . (Nov) 600
Soviet Health Care, Theodore B. Massell . . . . . (Oct) 475
Soviet Medicine, Alan P. Zelicoff . . . . . (Nov) 598
Tracheostomy Tube Failure, David M. Alessi, Gerald Berke . . . (Oct) 475
E. Fritz Schmerl . . . . . (Oct) 475
Two Articles in *WJM*, Marc Tunzi . . . . . (Sep) 339
Use and Safety of Miconazole During Pregnancy, Ronald E. Ainsworth . . . . . (Nov) 599
Reply, Peter J. Jewesson, Anthony W. Chow . . . . . (Nov) 599
Where Is the Pathologist?, C. Jack Bark . . . . . (Sep) 340
Reply, Helen M. Ranney . . . . . (Sep) 340
Wright's Law Is Right On, Gary Gorlick . . . . . (Sep) 340

Counseling Practices of Primary Care Physicians, see *Sexual History-Taking and*
Criteria for Brain Death (Correspondence), Lawrence F. Marshall . . . . . (Nov) 598

D

Death Penalty, see *Physicians and the*
Deaths From Firearms, see *Opposing Views on*
Dental Professionals and HIV Infection (Correspondence), L. Daniel Schaeffer, Harold A. Lubick, Steven H. Kleinman . . (Jul) 86
Dermatology, see *Epitomes*
Diabetes, Dietary Protein and Glomerular Hyperfiltration (Medical Staff Conference), Discussants: Burl R. Don, Morris Schambelan . . . . . (Oct) 449
Diabetic Lipemia With Fatty Splenomegaly Culminating in Unnecessary Splenectomy, James M. Small, Farhad Moatamed, Andrew Deiss, Dana E. Wilson . . . . . (Aug) 196
Diagnostic Value of Thyrotropin-Releasing-Hormone Stimulation in Patients With Pituitary Tumor (Clinical Investigation), David M. Cook, Monte A. Greer, H. Paxton . . . . . (Aug) 161
Dietary Protein and Glomerular Hyperfiltration, see *Diabetes*
Disseminated Actinomycosis, Eileen F. Hennrikus, Leigh Pederson . . . . . (Aug) 201
Diverticulitis of the Transverse Colon, see *Perforated*
Does a Helicopter Service Stimulate Financially Motivated Transfers? (Health Care Delivery), Kenneth J. Rhee, Robert J. O'Malley, James E. Turner, Neil H. Willits, Richard E. Ward . . . . . (Oct) 487
Drug Addicts, see *Hematogenously Acquired* Aspergillus *Vertebral Osteomyelitis in Seemingly Immunocompetent*
Duodenal Ulcer Disease—Lessons From History (Editorial), Edward Passaro, Jr . . . . . (Sep) 329
Duodenal Ulcer Disease, see *Recent Advances in the Treatment of*
Dystrophy Syndrome—Diagnosis and Management, see *Reflex Sympathetic*

E

Editorial Comment:

Controlling Perinatally Acquired HIV Infection, Martha F. Rogers (Jul) 109
'Moderate' Hypophosphatemia—Not Always an Innocent Bystander, R. Curtis Morris, Jr . . . . . (Nov) 577
Treatment of Acute Myocardial Ischemia, Robert B. Jennings . . . (Jul) 62

Editorials:

α_1-Antitrypsin—An Investigative Odyssey From the Benchtop to the Bedside, James E. Gadek . . . . . (Jul) 79
Are We a Violent Nation? . . . . . (Aug) 191
Are We Losing Ourselves Among the Trees? . . . . . (Jul) 80
Bacterial Meningitis in the 1980s, or One Drug or Many?, Charles E. Cherubin, Robert H. K. Eng . . . . . (Sep) 330
Battlefield Called Sarcoidosis, D. Geraint James . . . . . (Aug) 193
Chief Complaint . . . . . (Sep) 331
Coma After Cardiac Arrest—How Much Care Is Enough?, David E. Levy . . . . . (Aug) 191
Duodenal Ulcer Disease—Lessons From History, Edward Passaro, Jr . . . . . (Sep) 329
Geneticist's Grail, Edward M. Rubin, Yuet W. Kan . . . . . (Oct) 462
Health Policy Agenda for the American People . . . . . (Aug) 191
Light at the End of the Tunnel? . . . . . (Oct) 462
Nutrition During the Continuum of Development, Frank H. Morriss, Jr . . . . . (Oct) 463
Of Epidemics and Politicians . . . . . (Nov) 590
On Reducing Health Care Costs . . . . . (Sep) 329
Predictors of Physician Performance . . . . . (Jul) 79
Profession Responding to Stress . . . . . (Nov) 588
Sexual History-Taking, Marian Glasgow . . . . . (Aug) 194
Treatment of Obstructive Sleep Apnea—Who, When, How?, Eliot A. Phillipson . . . . . (Nov) 588

Electrolyte, Blood Urea Nitrogen and Glucose Level Screening in Medical Admissions—Impact on Patient Management (Clinical Investigation), Lloyd Rucker, F. Allan Hubbell, Barbara V. Akin, Elizabeth Frye . . . . . (Sep) 287
Correspondence, R. E. Horowitz . . . . . (Nov) 600
H. Braunstein . . . . . (Nov) 600
Emergency Services—Developing Valid Criteria, see *Categorization of Hospital*
Emerging Patterns of HIV Infection and Control in the Philippines (AIDS—A Global Perspective), Manuel M. Dayrit, Ofelia T. Monzon, Virginia Basaca-Sevilla, Curtis G. Hayes (Dec) 723
Encephalitis, see *Influenza B*

Epitomes:

Psychiatry:

Current Perspectives in Posttraumatic Stress Disorders, J. David Kinzie . . . . . (Jul) 71
Group Therapy and Schizophrenia, Nick Kanas . . . . . (Jul) 71
Update on Psychoneuroimmunology, George Freeman Solomon . . . . . (Jul) 72
Methods to Aid Memory in the Aged, Jerome A. Yesavage . . . . (Jul) 72
Environmental Sensitivity—Allergic to Everything?, Carroll M. Brodsky . . . . . (Jul) 73
Long-term Effects of Terrorism on Children, Spencer Eth . . . . . (Jul) 73
Children at Risk—New Aspects, Irving Philips . . . . . (Jul) 74
Family Involvement in Managing Schizophrenia, David Spiegel (Jul) 75
Childhood Depression—A Recent Phenomenon?, Irving N. Berlin (Jul) 75
Antidepressant Treatment for Bulimia, Joel Yager . . . . . (Jul) 75
The Dopamine Hypothesis Revisited, Allen R. Doran . . . . . (Jul) 76
Psychopharmacology of the Aged, Gary W. Small . . . . . (Jul) 76
Changing Trends in Accusations of Child Sexual Abuse, Graeme Hanson . . . . . (Jul) 77
Genetics of Mental Illness, Victor I. Reus . . . . . (Jul) 77

Urology:

New Developments in Diagnosing and Treating Erectile Impotence, Harin Padma-Nathan . . . . . (Aug) 187
The Continent Urinary Diversion, Stuart D. Boyd . . . . . (Aug) 187
Ureterorenoscopy, Jeffry L. Huffman . . . . . (Aug) 188
Integrated Management of Urinary Stone Disease, George W. Drach . . . . . (Aug) 188
Recent Advances in Diagnosing and Treating Prostatic Carcinoma, Arthur L. Dick . . . . . (Aug) 189
Lasers in Urology, J. A. Smith, Jr . . . . . (Aug) 189
Ultrasonography in Pediatric Urology Patients, J. David Moorhead . . . . . (Aug) 190
Treating Female Urinary Incontinence, Roger Hadley . . . . . (Aug) 190

Internal Medicine:

Use of Ipratropium Bromide in Chronic Obstructive Pulmonary Disease, Donald P. Tashkin . . . . . (Sep) 321
The Questionable Value of Routine Admission Urinalyses, F. Allan Hubbell, Barbara V. Akin . . . . . (Sep) 321
Correspondence, R. E. Horowitz . . . . . (Nov) 600
H. Braunstein . . . . . (Nov) 600
Diagnosing Pulmonary Embolism, Paul E. Bellamy . . . . . (Sep) 322
'Routine' Preoperative Laboratory Testing, Lawrence K. Loo . . (Sep) 323
Correspondence, R. E. Horowitz . . . . . (Nov) 600
H. Braunstein . . . . . (Nov) 600
Weight Control in Managing Hypertension, Kenneth A. Conrad, Joanne R. Conrad, Timothy C. Fagan . . . . . (Sep) 323
Relaxation Therapy for Hypertension, Eliseo J. Pérez-Stable . . . (Sep) 323

Postprandial Hypotension, Timothy C. Fagan, Kenneth A. Conrad . . . (Sep) 324
'Unloading' Therapy for Heart Failure, Kanu Chatterjee . . . (Sep) 324
Treatment of Gram-Negative Bacterial Meningitis, Larry J. Strausbaugh . . . (Sep) 325
Home Intravenous Antibiotic Therapy, John F. Trowbridge . . . (Sep) 325
Vaccination for Hepatitis B, Susan W. Tolle . . . (Sep) 326
Intraperitoneal Chemotherapy for Ovarian Cancer, Solomon Zimm . . . (Sep) 326
Bone Marrow Transplantation as Primary Treatment of Leukemia, Marek J. Bozdech . . . (Sep) 327
Physician-Patient Communication, Shiraz Mishra, Howard Waitzkin . . . (Sep) 328

Dermatology:

Removing Tattoos, Kenneth G. Gross . . . (Oct) 456
Lyme Disease, Denny L. Tuffanelli . . . (Oct) 457
Ketoconazole Use in Tinea Versicolor, Paul H. Jacobs . . . (Oct) 457
Recent Advances in Clinical Use of Retinoids, Nicholas J. Lowe . (Oct) 457
Liposuction in Dermatology, Samuel J. Stegman . . . (Oct) 458
Using Lasers in Skin Surgery, Norman Levine . . . (Oct) 458
Dysplastic Nevi—Markers and Precursors of Malignant Melanoma, William S. Crutcher . . . (Oct) 459
Contraindications for Using Topical Steroids, Roger C. Cornell . (Oct) 459
Bowenoid Papulosis, David A. South . . . (Oct) 460
Cutaneous Manifestations of the Acquired Immunodeficiency Syndrome (AIDS) and AIDS-Related Conditions, S. Ira Greene (Oct) 460
Short-Contact Anthralin Therapy for Psoriasis, Heidi E. Fleischmann . . . (Oct) 461

Radiology:

Angiographic Diagnosis and Therapy for Impotence, Joseph J. Bookstein, Alan Lurie . . . (Nov) 584
Duplex Sonographic Diagnosis of Deep Venous Thrombosis of the Leg, R. Brooke Jeffrey, Jr . . . (Nov) 584
Magnetic Resonance Imaging and Pelvic Abnormalities, Hedvig Hricak . . . (Nov) 585
Magnetic Resonance of the Liver, Albert A. Moss . . . (Nov) 585
Temporomandibular Joint Radiology Update, Joseph R. Thompson . . . (Nov) 586
Prenatal Diagnosis of Central Nervous System Abnormalities, Ronald R. Townsend, Roy A. Filly . . . (Nov) 586
Percutaneous Gastrostomy, Harold Coons . . . (Nov) 586
New Developments in Contrast Media, Sachiko T. Cochran . . . (Nov) 587

Ethnic Variability in Cholelithiasis—An Autopsy Study, Jose A. Arevalo, Alison Okada Wollitzer, Miguel Berry Corporon, Miriam Larios, David Huante, Maria Teresa Ortiz . . . (Jul) 44
Evaluation of the First 300 Patients Treated at an Outpatient Center for Male Sexual Dysfunction, Leland R. Ellis, Roger E. Nellans, Denise J. Kramer-Levien, Gayle Stewart Knoepfler, Peter Knoepfler . . . (Sep) 296
Exercise in the Elderly (Topics in Primary Care Medicine), Mary E. Wheat . . . (Oct) 477

F

Fear of the Unknown (Correspondence), Ira E. Bailie . . . (Oct) 475
Fetus and Newborn, see *Nutrition of the*
Financing Options for Long-term Care, see *Private*
Firearms, see *Opposing Views on*
First Case (Original Essay), Henry Schneiderman . . . (Nov) 623
French National Program for the Prevention and Control of AIDS (AIDS—A Global Perspective), Alain Pompidou . . . (Dec) 730

G

Gallbladder in Cholecystectomy Patients, see *Oral Cholecystography and Sonography of*
Gene Identification in Humans, see *Mapping Approaches to*
Geneticist's Grail (Editorial), Edward M. Rubin, Yuet W. Kan . . (Oct) 462
Genetic Markers in Huntington's Disease (Commentary), Elliot M. Frohman, Joseph B. Martin . . . (Oct) 486
Global Epidemiology (AIDS—A Global Perspective), C. Fordham von Reyn, Jonathan M. Mann . . . (Dec) 694
Glomerular Hyperfiltration, see *Diabetes, Dietary Protein and*
Glucose Level Screening in Medical Admissions—Impact on Patient Management, see *Electrolyte, Blood Urea Nitrogen and*
Grocery Checkers, see *Carpal Tunnel Syndrome in*
Group B Streptococcal Soft Tissue Infections Beyond the Neonatal Period, James M. McCarty, Judy Haber . . . (Nov) 558
Guidelines for the Control of Perinatally Transmitted Human Immunodeficiency Virus Infection and Care of Infected Mothers, Infants and Children (Special Article), George W. Rutherford, Geraldine E. Oliva, Moses Grossman, James R. Green, Diane W. Wara, Nancy S. Shaw, Dean F. Echenberg, Constance B. Wofsy, Daniel H. Weinstein, Florence Stroud, Edwin S. Sarsfield, David Werdegar . . . (Jul) 104
Editorial Comment, Martha F. Rogers . . . (Jul) 109
Correspondence, Jeffrey S. Greenspoon, Gerald S. Bernstein . (Nov) 600
Gunshot Wound, see *Traumatic Hypopituitarism Due to a*

H

Health Care Delivery:

House Calls in Utah, Mark S. Schueler, Dona L. Harris, Gerald K. Goodenough, Linda Collette . . . (Jul) 92
Does a Helicopter Service Stimulate Financially Motivated Transfers?, Kenneth J. Rhee, Robert J. O'Malley, James E. Turner, Neil H. Willits, Richard E. Ward . . . (Oct) 487
Categorization of Hospital Emergency Services—Developing Valid Criteria, R. Myles Riner, Kathryn Maino Collins, Garrett E. Foulke, George V. Moorhead, Phillip Terry . . . (Nov) 602

Health Care System, see *Soviet*
Health Policy Agenda for the American People (Editorial) . . . . (Aug) 191
Heart Disease and Mortality (Correspondence), James C. Roberts, Jr . . . (Aug) 206
Heart With Cerebral Metastases, see *Rhabdomyosarcoma of the*
Helicopter Service Stimulate Financially Motivated Transfers?, see *Does a*
Hematogenously Acquired *Aspergillus* Vertebral Osteomyelitis in Seemingly Immunocompetent Drug Addicts, David L. Brown, Daniel M. Musher, George E. Taffet . . . (Jul) 84
Hepatitis B Vaccination, see *Asthma and Urticaria After*
Heterosexual HIV Infection, see *Condom Use*
History-Taking and Counseling Practices of Primary Care Physicians, see *Sexual*
HIV Infection, see *Condom Use*
HIV Infection, see *Controlling Perinatally Acquired*
HIV Infection, see *Dental Professionals and*
HIV Infection in Adults, see *Clinical Manifestations and the Natural History of*
Hospital Emergency Services—Developing Valid Criteria, see *Categorization of*
Hospitals, see *Plight of Public*
House Calls in Utah (Health Care Delivery), Mark S. Schueler, Dona L. Harris, Gerald K. Goodenough, Linda Collette . . . . . (Jul) 92
How Physicians Can Improve Patients' Participation and Maintenance in Self-Care (Seminars in Health Care Delivery), Lawrence W. Green . . . (Sep) 346
Human Immunodeficiency Virus and Related Retroviruses (AIDS—A Global Perspective), Rafael Nájera, M. I. Herrera, R. de Andrés . . . (Dec) 702
Humanistic Performance, see *Sociodemographic and Premedical School Factors Related to Postgraduate Physicians'*
Huntington's Disease, see *Genetic Markers in*
Hypernatremia Associated With Cathartics in Overdose Management, John W. Caldwell, Adolph J. Nava, David D. de Haas . . . . . (Nov) 593
Hypocalcemia in Normomagnesemic Patients, see *Low Blood Mononuclear Cell Magnesium Content and*
Hypomagnesemia (Correspondence), Edmund B. Flink, Jerry K. Aikawa, Robert Whang, Warren E. C. Wacker . . . . . (Jul) 86
Hypophosphatemia, see *'Moderate'*
Hypopituitarism Due to a Gunshot Wound, see *Traumatic*

I

Immunodeficiency Virus Infection and Care of Infected Mothers, Infants and Children, see *Guidelines for the Control of Perinatally Transmitted Human*
Infections of the Central Nervous System, see *Chemotherapy for Bacterial*
Influenza B Encephalitis, William H. Bayer . . . (Oct) 466

Information:
Endoscopic Sclerotherapy for Esophageal Varices, Harvey S. Young . . . . . (Sep) 359

Insects in the Operating Room (Correspondence), Ronald A. Sherman, James Spiegel, Regina F. Gandour . . . . . (Sep) 340
John Blossom . . . . . (Nov) 601
Internal Medicine, see *Epitomes*

J

Japan, see *AIDS Prevention and Control in*

L

Laws for Minors in the Western United States, see *Consent and Confidentiality*
Light at the End of the Tunnel? (Editorial) . . . . . (Oct) 462
Lipemia With Fatty Splenomegaly Culminating in Unnecessary Splenectomy, see *Diabetic*
Liver Diseases, see *Lung and*
Long-term Care, see *Private Financing Options for*
Low Blood Mononuclear Cell Magnesium Content and Hypocalcemia in Normomagnesemic Patients (Clinical Investigation), Elizabeth Ryzen, Tony A. Nelson, Robert K. Rude . . . . . (Nov) 549
Lung and Liver Diseases, see *Association of α_1-Antitrypsin Deficiency With*
Lymphadenectomy, see *Pelvic Fullness, Urgency and Frequency Following*

M

Malaria From Mexico—A Problem in the United States, see *Plasmodium vivax*
Male Sexual Dysfunction, see *Evaluation of the First 300 Patients Treated at an Outpatient Center for*
Mapping Approaches to Gene Identification in Humans (Clinical Investigation), Raymond L. White, Jean-Marc Lalouel, G. Mark Lathrop, Mark F. Leppert, Yusuke Nakamura, Peter O'Connell . . . . . (Oct) 423
Editorial, Edward M. Rubin, Yuet W. Kan . . . . . (Oct) 462
Maxillary Sinusitis—The Focus of Toxic Shock Syndrome in a Male Patient, Stephen D. Wood, Kristen Ries, George L. White, Richard T. Murdock, Donald M. Pedersen . . . . . (Oct) 467

Medical Education:
Sociodemographic and Premedical School Factors Related to Postgraduate Physicians' Humanistic Performance, Lawrence S. Linn, Dennis W. Cope, Alan Robbins . . . . . (Jul) 99
Editorial . . . . . (Jul) 79
Sufficiency of Clinical Literature on the Appropriate Uses of Six Medical and Surgical Procedures, Arlene Fink, Robert H. Brook, Jacqueline Kosecoff, Mark R. Chassin, David H. Solomon . . (Nov) 609

Medical Progress:
Association of α_1-Antitrypsin Deficiency With Lung and Liver Diseases, Mariela Resendes . . . . . (Jul) 48
Editorial, James E. Gadek . . . . . (Jul) 79
Pathogenesis of Sarcoidosis, Karl Van Gundy, Om P. Sharma . . (Aug) 168
Editorial, D. Geraint James . . . . . (Aug) 192
Recent Advances in the Treatment of Duodenal Ulcer Disease—A Surgical Perspective, Michael W. Mulholland . . . . . (Sep) 301
Editorial, Edward Passaro, Jr . . . . . (Sep) 329
Nutrition of the Fetus and Newborn, Jan M. Kennaugh, William W. Hay, Jr . . . . . (Oct) 435
Editorial, Frank H. Morriss, Jr . . . . . (Oct) 463
Treatment of the Obstructive Sleep Apnea Syndrome, Robert V. Wiggins, Wolfgang W. Schmidt-Nowara . . . . . (Nov) 561
Editorial, Eliot A. Phillipson . . . . . (Nov) 588

Medical Schools of the West:
Oregon Health Sciences University School of Medicine Celebrates Centennial, Fred W. Leonhardt, Darrell E. Ward . . . . . (Oct) 481

Medical Staff Conferences:
Biochemical and Clinical Aspects of Amyloidosis, Discussants: Diane Havlir, Lawrence Tierney, Jr . . . . . (Jul) 65
New Approaches to Treating Systemic Lupus Erythematosus, Discussant: David Wofsy . . . . . (Aug) 181
Asthma Mortality, Discussants: Homer A. Boushey, Joni Nichols (Sep) 314
Diabetes, Dietary Protein and Glomerular Hyperfiltration, Discussants: Burl R. Don, Morris Schambelan . . . . . (Oct) 449
Advances in the Prenatal Diagnosis of Sickle Cell Anemia, Discussant: Stephen H. Embury . . . . . (Nov) 580

Medicare-Funded Cardiac Transplants (Correspondence), Brian E. Jaski, Sidney C. Smith, Walter P. Dembitsky . . . . . (Aug) 206

Medicine in Perspective:
Soviet Health Care System, David S. Friedenberg . . . . . (Aug) 214
Correspondence, Theodore B. Massell . . . . . (Oct) 475
Correspondence, Alan P. Zelicoff . . . . . (Nov) 598

Meningitis—A Retrospective Analysis of Cases Reported in the United States, 1970-1979, see *Plague*
Meningitis in the 1980s, or One Drug or Many?, See *Bacterial*
Methyl Bromide and Chloropicrin, see *Acute Symptoms in Persons Residing Near a Field Treated With the Soil Fumigants*
Miconazole During Pregnancy, see *Use and Safety of*
Minors in the Western United States, see *Consent and Confidentiality Laws for*
'Moderate' Hypophosphatemia—Not Always an Innocent Bystander (Editorial Comment), R. Curtis Morris, Jr . . . . . (Nov) 577
More Insects in the Operating Room (Correspondence), John Blossom . . . . . (Nov) 601
Myocardial Ischemia, see *Treatment of Acute*

N

Neonatal Period, see *Group B Streptococcal Soft Tissue Infections Beyond the*
Neurologic Sequelae of Cardiac Arrest (Specialty Conference), Discussant: W. T. Longstreth, Jr . . . . . (Aug) 175
Editorial, David E. Levy . . . . . (Aug) 193
New Approaches to Treating Systemic Lupus Erythematosus (Medical Staff Conference), Discussant: David Wofsy . . . . . (Aug) 181
Newborn, see *Nutrition of the Fetus and*
New World With AIDS—Health Promotion as a Catalyst for Change (AIDS—A Global Perspective), Anthony J. Meyer . . . . . (Dec) 716
Normomagnesemic Patients, see *Low Blood Mononuclear Cell Magnesium Content and Hypocalcemia in*
Nutrition of the Fetus and Newborn (Medical Progress), Jan M. Kennaugh, William W. Hay, Jr . . . . . (Oct) 435
Editorial, Frank H. Morriss, Jr . . . . . (Oct) 463

O

Obstructive Sleep Apnea, see *Tracheostomy Tube Failure in*
Obstructive Sleep Apnea Syndrome, see *Treatment of*
Of Epidemics and Politicians (Editorial) . . . . . (Nov) 590
On Reducing Health Care Costs (Editorial) . . . . . (Sep) 329
Operating Room, see *Insects in*
Opposing Views on Deaths From Firearms (Correspondence), Alexander C. Johnson . . . . . (Aug) 207
Matthew L. Howard . . . . . (Aug) 207
Reply, Garen J. Wintemute, Stephen P. Teret, Jess F. Kraus . (Aug) 208
Oral Cholecystography and Sonography of Gallbladder in Cholecystectomy Patients, Antonio Robles, Daniel Devor, Hansen Wang, Charles Warren . . . . . (Oct) 432
Oregon Health Sciences University School of Medicine Celebrates Centennial (Medical Schools of the West), Fred Leonhardt, Darrell E. Ward . . . . . (Oct) 481

Original Essay:
First Case, Henry Schneiderman . . . . . (Nov) 623

Overdose Management, see *Hypernatremia Associated With Cathartics*
Overuse of Health Resources by Penicillin-Sensitive Children (Correspondence), Charles A. Pilcher . . . . . (Sep) 339

P

Pain Control in Cancer Patients (Correspondence), Amber Arlington . . . (Oct) 474
Reply, Malcolm L. Brigden, Jeffrey B. Barnett . . . (Oct) 474
Pasteurella multocida Urinary Tract Infection, Bruce A. Mann, Ronald W. Quenzer . . . (Aug) 200
Pathogenesis of Sarcoidosis, Karl Van Gundy, Om P. Sharma (Medical Progress) . . . (Aug) 168
Editorial, D. Geraint James . . . (Aug) 192
Pathologist, see *Where is the*
Patients' Participation and Maintenance in Self-Care, see *How Physicians Can Improve*
Patterns of Cervical Spine Injury and Their Associated Lesions, A. Norman Guthkelch, Alan S. Fleischer . . . (Oct) 428
Pelvic Fullness, Urgency and Frequency Following Lymphadenectomy (Radiologic Case), Renee A. Spiegel, Samuel J. Hessel, Edward R. Katz, Jonathan M. Levy . . . (Sep) 357
Penicillin-Sensitive Children, see *Overuse of Health Resources by*
Perforated Diverticulitis of the Transverse Colon, Michael D. Peck, Hugo V. Villar . . . (Jul) 81
Perinatally Acquired HIV Infection, see *Controlling*
Perinatally Transmitted Human Immunodeficiency Virus Infection and Care of Infected Mothers, Infants and Children, see *Guidelines for the Control of*
Peripheral Blood and Bone Marrow Abnormalities in the Acquired Immunodeficiency Syndrome (Clinical Investigation), Michael Frontiera, Adam M. Myers . . . (Aug) 157
Philippines, see *Emerging Patterns of HIV Infection and Control in the*
Phosphorus and Water (Correspondence), Carolyn Csongradi . . (Nov) 601
Phosphorus Metabolism, see *Clinical Disorders of*
Physicians and the Death Penalty (Correspondence), Todd C. Grey, E. S. Sweeney . . . (Aug) 207
David L. Wishart . . . (Aug) 207
Physicians' Humanistic Performance, see *Sociodemographic and Premedical School Factors Related to Postgraduate*
Pituitary Tumor, see *Diagnostic Value of Thyrotropin-Releasing-Hormone Stimulation in Patients With*
Plague Meningitis—A Retrospective Analysis of Cases Reported in the United States, 1970-1979, Thomas M. Becker, Jack D. Poland, Thomas J. Quan, Mark E. White, Jonathan M. Mann, Allan M. Barnes . . . (Nov) 554
Plasmodium vivax Malaria From Mexico—A Problem in the United States, Judith Brillman . . . (Oct) 469
Plight of Public Hospitals (Correspondence), Ralph C. Jung . . . (Aug) 205
Postgraduate Physicians' Humanistic Performance, see *Sociodemographic and Premedical School Factors Related to*
Predictors of Physician Performance (Editorial) . . . (Jul) 79
Pregnancy, see *Use and Safety of Miconazole During*
Premedical School Factors Related to Postgraduate Physicians' Humanistic Performance, see *Sociodemographic and*
Prenatal Diagnosis of Sickle Cell Anemia, see *Advances in the*
Preventive Care Screening for Adolescents—What About Substance Abuse Screening? (Correspondence), Richard Ries . . . (Jul) 86
Primary Care—Does It Have a Future? (Correspondence), William W. Johnson . . . (Sep) 339
Primary Care Physicians, see *Sexual History-Taking and Counseling Practices of*
Private Financing Options for Long-term Care (Special Article), Barbara L. Brody, Harold J. Simon, Dennis E. Smallwood . . . (Sep) 350
Profession Responding to Stress (Editorial)Nov 588
Psychiatry, see *Epitomes*

Public Health:

Acute Symptoms in Persons Residing Near a Field Treated With the Soil Fumigants Methyl Bromide and Chloropicrin, Lynn R. Goldman, Donald Mengle, David M. Epstein, Deloris Fredson, Kem Kelly, Richard J. Jackson . . . (Jul) 95
Chemical Contamination of California Drinking Water, Hanafi H. Russell, Richard J. Jackson, David P. Spath, Steven A. Book . . . (Nov) 615

Radiologic Case:

Pelvic Fullness, Urgency and Frequency Following Lymphadenectomy, Rence A. Spiegel, Samuel J. Hessel, Edward R. Katz, Jonathan M. Levy . . . (Sep) 357
Radiology, see *Epitomes*
Recent Advances in the Treatment of Duodenal Ulcer Disease—A Surgical Perspective (Medical Progress), Michael W. Mulholland . . . (Sep) 301
Editorial, Edward Passaro, Jr . . . (Sep) 329
Reflex Sympathetic Dystrophy Syndrome—Diagnosis and Management (Topics in Primary Care Medicine), David L. Smith, Stephen M. Campbell . . . (Sep) 342
Rhabdomyosarcoma of the Heart With Cerebral Metastases, Stanley J. Geyer . . . (Nov) 596
Right Way to Go (Commentary), E. R. W. Fox . . . (Aug) 225
Sarcoidosis, see *Battlefield Called*
Sarcoidosis, see *Pathogenesis of*
'Screening' and 'Routine' Testing (Correspondence), R. E. Horowitz . . . (Nov) 600
H. Braunstein . . . (Nov) 600
Self-Care, see *How Physicians Can Improve Patients' Participation and Maintenance in*

Seminars in Health Care Delivery:

How Physicians Can Improve Patients' Participation and Maintenance in Self-Care, Lawrence W. Green . . . (Sep) 346
Sexual Dysfunction, see *Evaluation of the First 300 Patients Treated at an Outpatient Center for*
Sexual History-Taking and Counseling Practices of Primary Care Physicians, Charles E. Lewis, Howard E. Freeman . . . (Aug) 165
Editorial, Marian Glasgow . . . (Aug) 194
Sickle Cell Anemia, see *Advances in the Prenatal Diagnosis of*
Sinusitis, see *Maxillary*
Sleep Apnea, see *Tracheostomy Tube Failure in Obstructive*
Sleep Apnea Syndrome, see *Treatment of Obstructive*
Social, Cultural and Demographic Aspects of AIDS (AIDS—A Global Perspective), Renée Sabatier . . . (Dec) 713
Sociodemographic and Premedical School Factors Related to Postgraduate Physicians' Humanistic Performance (Medical Education), Lawrence S. Linn, Dennis W. Cope, Alan Robbins (Jul) 99
Editorial . . . (Jul) 79
Somatizing Patients, see *Treating*
Soviet Health Care System (Medicine in Perspective), David S. Friedenberg . . . (Aug) 214
Correspondence, Theodore B. Massell . . . (Oct) 475
Alan P. Zelicoff . . . (Nov) 598
Space Medicine—A Review of Current Concepts, Tony E. Vasquez, Harold T. Pretorius, Daniel S. Rimkus . . . (Sep) 292

Special Articles:

Guidelines for the Control of Perinatally Transmitted Human Immunodeficiency Virus Infection and Care of Infected Mothers, Infants and Children, George W. Rutherford, Geraldine E. Oliva, Moses Grossman, James R. Green, Diane W. Wara, Nancy S. Shaw, Dean F. Echenberg, Constance B. Wofsy, Daniel H. Weinstein, Florence Stroud, Edwin S. Sarsfield, David Werdegar . . . (Jul) 104
Editorial Comment, Martha F. Rogers . . . (Jul) 109
Correspondence, Jeffrey S. Greenspoon, Gerald S. Bernstein (Nov) 600
Consent and Confidentiality Laws for Minors in the Western United States, Lawrence S. Neinstein . . . (Aug) 218
Private Financing Options for Long-term Care, Barbara L. Brody, Harold J. Simon, Dennis E. Smallwood . . . (Sep) 350

Specialty Conferencs:

Cardiac Ischemia. Part II—Reperfusion and Treatment (UCLA Interdepartmental Conference), Moderator: Glenn A. Langer; Discussants: Gerald D. Buckberg, Jan H. Tillisch . . . (Jul) 54
Editorial Comment, Robert B. Jennings . . . (Jul) 62
Neurologic Sequelae of Cardiac Arrest, Discussant: W. T. Longstreth, Jr . . . (Aug) 175
Editorial, David E. Levy . . . (Aug) 193
Splenectomy, see *Diabetic Lipemia With Fatty Splenomegaly Culminating in Unnecessary*
Stress, see *Profession Responding to*
Substance Abuse Screening, see *Preventive Care Screening for Adolescents*

Sufficiency of Clinical Literature on the Appropriate Uses of Six Medical and Surgical Procedures (Medical Education), Arlene Fink, Robert H. Brook, Jacqueline Kosecoff, Mark R. Chassin, David H. Solomon . . . . . (Nov) 609
Systemic Lupus Erythematosus, see *New Approaches to Treating*

T

Testing, see *'Screening' and 'Routine'*
Thrombophlebitis of the Superior Vena Cava Caused by *Candida glabrata*, see *Catheter-Related*
Thyrotropin-Releasing-Hormone Stimulation in Patients With Pituitary Tumor, see *Diagnostic Value of*

Topics in Primary Care Medicine:

Treating Somatizing Patients, Geoffrey H. Gordon . . . . . (Jul) 88
Clinical Significance and Interpretation of Anti-nuclear Antibodies, Richard H. White, Dick L. Robbins . . . . . (Aug) 210
Reflex Sympathetic Dystrophy Syndrome—Diagnosis and Management, David L. Smith, Stephen M. Campbell . . . . . (Sep) 342
Exercise in the Elderly, Mary E. Wheat . . . . . (Oct) 477

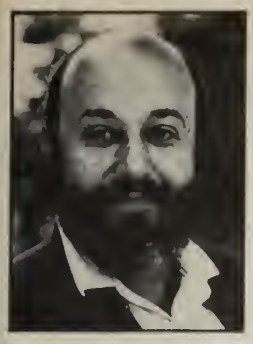
Towards a National AIDS-Control Program in Uganda (AIDS—A Global Perspective), Samuel Ikwaras Okware . . . . . (Dec) 726
Toxic Shock Syndrome in a Male Patient, see *Maxillary Sinusitis*
Tracheostomy Tube Failure in Obstructive Sleep Apnea, David M. Rodman, Richard J. Martin . . . . . (Jul) 41
Correspondence, David M. Alessi, Gerald Berke . . . . . (Oct) 475
E. Fritz Schmerl . . . . . (Oct) 475
Traumatic Hypopituitarism Due to a Gunshot Wound, Daniel Trujillo-Juarez, Floyd L. Culler, Robert S. Ganelin, Kenneth L. Jones . . . . . (Nov) 591
Treating Somatizing Patients (Topics in Primary Care Medicine), Geoffrey H. Gordon . . . . . (Jul) 88
Treatment of Acute Myocardial Ischemia (Editorial Comment), Robert B. Jennings . . . . . (Jul) 62
Treatment of the Obstructive Sleep Apnea Syndrome (Medical Progress), Robert V. Wiggins, Wolfgang W. Schmidt-Nowara (Nov) 561
Editorial, Eliot A. Phillipson . . . . . (Nov) 588
Tuberculoma of the Brain Stem, Patrick D. Lyden . . . . . (Aug) 198
Two Articles in *WJM* (Correspondence), Marc Tunzi . . . . . (Sep) 339

U

Uganda, see *Towards a National AIDS-Control Program in*
Ulcer Disease—A Surgical Perspective, see *Recent Advances in the Treatment of Duodenal*
Urinary Tract Infection, see Pasteurella multocida
Urology, see *Epitomes*
Urticaria After Hepatitis B Vaccination, see *Asthma and*
Use and Safety of Miconazole During Pregnancy (Correspondence), Ronald E. Ainsworth . . . . . (Nov) 599
Reply, Peter J. Jewesson, Anthony W. Chow . . . . . (Nov) 599
Utah, see *House Calls in*

W

Water, see *Chemical Contamination of California Drinking*
Where Is the Pathologist? (Correspondence), C. Jack Bark . . . . (Sep) 340
Reply, Helen M. Ranney . . . . . (Sep) 340
Work-Related Illness, see *Carpal Tunnel Syndrome in Grocery Checkers*
World Health Organization's Global Strategy for the Prevention and Control of AIDS (AIDS—A Global Perspective), Jonathan M. Mann . . . . . (Dec) 732
Wound Botulism, Jay Swedberg, Thomas H. Wendel, Frederick Deiss . . . . . (Sep) 335
Wright's Law Is Right On (Correspondence), Gary Gorlick . . . (Sep) 340



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* Joseph Lee, M.D. ▶
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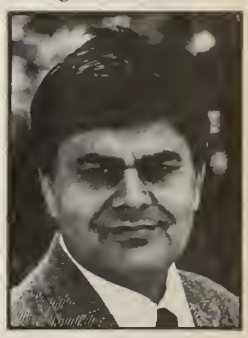

CONTINUING MEDICAL EDUCATION

(Continued from Page 688)

January 21-22—**Transportation of Hazardous Materials/Waste.** USC. Thur-Fri. $265. Contact: USC.

January 25-29—**Hazardous Materials: Handling and Disposal.** USC. Mon-Fri. $735. Contact: USC.

February 1—**Hazardous Waste Management of Small Generators.** USC. Mon. 1 hr. $160. Contact: USC.

February 2-4—**11th Annual: Neurology for Non-Neurologists.** UCSD and Neurology for Non-Neurologists Foundation at Holiday Inn Embarcadero, San Diego. Tues-Thurs. 21 hrs. $395. Contact: Edith S. Bookstein/NNN, PO Box 3586, La Jolla 92038. (619) 454-3212.

February 3-5—**Clinical Laboratory Molecular Analysis: Future Perspectives.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Wed-Fri. 24 hrs. Contact: Bonny Mower, Box 400s, Scripps Clinic and Research Foundation, 10666 N Torrey Pines, Rd, La Jolla 92037. (619) 457-8556.

February 8-12—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

February 8-13—**The UCI Family Practice Refresher Course.** The Center for Health Education at Newport Sheraton, Newport Beach. Mon-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., P.O. Box 1428, Long Beach, 90801-1428. (213) 595-3811.

February 11-12—**Back Injury Prevention.** USC. Thur-Fri. $280. Contact: USC.

February 11-13—**21st Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

February 12-13—**Comprehensive Care of the AIDS Patient: A Workshop.** UCSF. Fri-Sat. Contact: UCSF.

February 13-15—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs. Sat-Mon. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262. (619) 325-5588.

February 15-17—**Recent Advances in Geriatric Rehabilitation: What Is It? Who Needs It? What Works?** UCSD at Holiday Inn at the Embarcadero, San Diego. Mon-Wed. 18 hrs. $295. Contact: UCSD.

February 15-17—**8th Annual Betty Ford Center Conference on Alcoholism/Chemical Dependency: Integrating Concerns in Chemical Dependency.** Annenberg Center for Health Sciences and the Betty Ford Center. Mon-Wed. 13.5 hrs. Contact: Annenberg Center, 39000 Bob Hope Drive, Rancho Mirage 92270-3298. (800) 321-3690-national; (800) 621-7322-Calif.

February 15-17—**Clinical Hematology and Oncology: 1988.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

February 18-19—**Video Display Terminal Safety.** USC. Thur-Fri. $265. Contact: USC.

February 19-21—**Diagnosis and Management of Respiratory Disease.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. 11-13 hrs. $225-$295. Contact: MER, 5808 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

February 19-21—**New Precepts and Concepts in Dermatopathology.** Desert Hospital, Palm Springs at Desert Hospital. Fri-Sun. 14 hrs. $350. Contact: Charles Steffen, MD, 1111 Tahquitz East, Ste 102A, Palm Springs 92262.

March 2-5—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Stanford Court Hotel, San Francisco. Wed-Sat. 17 hrs. Contact: UCSF.

March 4—**14th Annual Diabetes Program.** UCD at Capitol Plaza Holiday Inn, Sacramento. Contact: UCD.

March 4-9—**Western Scientific Assembly.** CMA at Bally's Hotel, Reno, Nevada. Thur-Sun. Contact: Susan Schaefer, CMA, P.O. Box 7690, San Francisco, 94120-7690. (415) 863-5522 Ext. 404.

(Continued on Page 758)

CONTINUING MEDICAL EDUCATION

(Continued from Page 757)

March 4-10—**56th Annual Postgraduate Convention.** LLU. Fri-Thur. 35 hrs. Contact: LLU.

March 11-12—**Sleep Disorders Medicine: Medical Management.** Scripps Clinic and Research Foundation. Fri-Sat. 12 hrs. $200. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

March 11-12—**Diabetes Update.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sat. Contact: UCSF.

March 16-19—**5th Annual Horizon in Reproductive Health Medical Conference.** UCSD at Hotel Del Coronado, Coronado. Wed-Sat. Contact: Mary Fessel, 2100 5th Ave., San Diego, 90101. (619) 231-6760.

March 18-19—**Hematology: Neonatal, Pediatric and AIDS Related Issues.** Children's Hospital, Oakland at Berkeley Marina Marriott Hotel. Fri-Sat. 11 hrs. Contact: Kim Leadon, CME Department, Children's Hospital, 747 52nd St, Oakland 94609. (415) 428-3021.

March 19—**Impatient Vs. Outpatient Treatment: How to Decide.** California Society for the Treatment of Alcoholism & Other Drug Dependencies at Ramada Renaissance Hotel, San Francisco. Sat. Contact: Corinne Parker, 3803 Broadway, Suite 2, Oakland, 94611. (415) 428-9091.

March 19-21—**Transfusion—Associated Infections and Immune Response.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. Contact: UCSF.

March 26-April 2—**Orthopedic Emergencies.** Scripps Memorial Hospital, Encinitas and American Institute of Postgraduate Education at Waiohai and Poipu Beach Hotels, Kauai. One week. 21 hrs. $395. Contact: Edith S. Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 26-April 2—**Behavioral Medicine for the Family Physician.** University of Arizona at Kona, Hawaii. One week. 24 hrs. Contact: Kathy Rairigh, Epic Expeditions, P.O. Box 209, Sun Valley, Idaho 83353. (208) 788-4995.

April 10-15—**Advanced Methods in Pharmacokinetics and Pharmacodynamics.** UCSF. Sun-Fri. Contact: UCSF.

April 13-15—**9th Annual Advances in Infectious Diseases: Current Therapy.** UCSF at Sheraton-Palace Hotel, San Francisco. Wed-Fri. 16 hrs. $365. Contact: UCSF.

April 13-17—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Desert Princess Resort, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

April 15-17—**Office Orthopedics for the Primary Care Physicians.** CMEA & Sharp Memorial Hospital at San Diego Princess Hotel. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego, 92138. (619) 223-2997.

April 23—**Current Concepts in Liver Diseases.** Scripps Clinic and Research Foundation at Amphitheater, Scripps Clinic, La Jolla. Thur. 6 hrs. $125. Contact: Bonny Mower, 10666 N. Torrey Pines Road, La Jolla, 92037. (619) 457-8556.

May 6-8—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Ceasars Palace, Las Vegas, Nevada. Fri-Sun. 11-13 hrs. $225-$295. Contact: MER, 5080 S. Rapp St., Suite 202, Littleton, CO 80120. (800) 421-3756.

May 26-27—**Current Concepts of Anatomic Pathology.** UCSF. Thur-Fri. Contact: UCSF.

June 13-17—**Family Practice Refresher Course.** UCI at Sheraton Newport, Newport Beach. Mon-Fri. 44.5 hrs. $575. Contact: UCI.

June 18-19—**Skills Workshop: Flexible Sigmoidoscopy and Colposcopy.** UCI at Sheraton Newport, Newport Beach. Sat-Sun. 16 hrs. $140-ea., $250-both. Contact: UCI.

July 15-18—**Caring for People with AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

IDAHO

February 13-20—**Controversies in Pulmonary Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

February 20-27—**Effective Treatment of Common Sports Injuries.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 4-6—**29th Annual Medical Winter Clinics—"You and Your Health."** Ada County Medical Society at Shore Lodge—Brundage Mountain for Alpine Powder and Nordic Skiing, McCall, Idaho. Fri-Sun. 11 hrs. $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 12-19—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

January 8-15—**Controversies in Wilderness Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Big Sky. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

February 18-20—**7th Annual Big Sky Pulmonary Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Thurs-Sat. Contact: ALA of Montana, 825 Helena Ave, Helena 59601. (406) 442-6556 or 1 (800) 252-6368 (in Montana).

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 5-March 1—**History of Medicine Seminar—Modern Medicine.** David A. Bennahum, MD, Instructor. Medical Center Library, University of New Mexico, Albuquerque. 4-6 pm, Tuesdays.

January 15-17—**Essentials of Health Care for Elderly: Clinical Evaluation and Management** (Session II). UNM Conference Center, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

January 28-29—**Humane Care and Use of Laboratory Animals.** Sheraton Old Town, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 12-14—**Case Studies in Cardiology.** Presbyterian Heart Institute, Albuquerque. Contact: (505) 841-1065/(505) 242-2796.

February 25-27—**21st Annual OB/GYN Postgraduate Seminar.** Holiday Inn Pyramid Plaza, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 25-27—**Santa Fe Ski Symposium—Hypertension—1988.** Santa Fe. Thurs-Sat. Contact: National Kidney Foundation of New Mexico, 1715 Girard, NE, Albuquerque 87106. (505) 266-4573.

February 26-28—**16th Annual Thoracic Society Lung Disease Symposium.** Santa Fe Hilton. Fri-Sun. Contact: Lung Association, (505) 265-0732.

(Continued on Page 759)

(Continued from Page 758)

March 4-5—**Advances in Internal Medicine '88.** Veterans Administration Medical Center. Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

March 11—**The Physician in Crisis.** Presbyterian Hospital Quality of Life Committee. Contact: Office of Medical Education, (505) 841-1225.

March 12—**NM Pediatric Society Wylder Lecture—Mother to Child Infection.** UNM School of Pharmacy Auditorium. Contact: Marilyn Stark, NM Pediatric Society, (505) 265-7431.

April 21-23—**10th Annual Pediatric Cardio-Pulmonary Update.** Sheraton Old Town, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

April 29-May 1—**Southwest Allergy Forum.** Eldorado Hotel, Sante Fe. Contact: UNM SOM, Office of CME, (505) 277-3942.

May 5-7—**NM Medical Society Annual Meeting—AIDS—Protecting the Health Professional and Chemical Dependency, Monitored Treatment Program. Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Albuquerque Hilton Inn. Contact: NM Medical Society, (505) 266-7868.

May 14—**Cardiac Physical Diagnosis Symposium.** Contact: UNM SOM, Office of CME, (505) 277-3942.

May 19-20—**Mental Health Services With Hispanic and Native American Children and Families.** Contact: UNM SOM, Office of CME, (505) 277-3942.

June 2-3—**8th Annual UNM/ACEP Emergency Medicine Symposium.** AMFAC Hotel, Albuquerque. Contact: UNM SOM, Office of CME, (505) 277-3942.

July 22-24—**Diagnosis and Management of Arrhythmia.** Contact: Presbyterian Heart Institute, Albuquerque, (505) 841-1065/(505) 242-2796.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

(Continued on Page 760)

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Waiting Period: ☐ 30 Days ☐ 60 Days ☐ 90 Days ☐ 180 Days ☐ Year

Disability Insurance Services, Inc.
887 Oak Grove, Suite 201, Menlo Park, CA 94025

Toll Free — Weekdays 1 800 551-1985

CONTINUING MEDICAL EDUCATION

(Continued from Page 759)

January 6-10—**4th Annual Hip-Knee Bioskills Workshop** (Sponsor: UUMC). Wed-Sun. Snowbird Cliff Lodge. Contact: Rosalie Lammle, (801) 581-8664.

January 15-16—**Psychiatric Gerontology: Depression in the Elderly** (Sponsor: UUMC). Fri-Sat. University Park Hotel, Salt Lake City. 12 hrs. Contact: Rosalie Lammle, (801) 581-8664.

January 16-18—**Arthroscopic Surgery 1988** (Sponsor: UUMC). Sat-Mon. Snowbird Resort. Contact: Robert Metcalf, MD, (801) 581-7601.

January 19-21—**Pulmonary Function Testing** (Sponsor: UUMC). Tues-Thurs. Contact: Connie Crandall, (801) 581-5710.

January 29-31—**Contemporary Approaches to Sexual Function/Dysfunction** (Sponsor: UUMC). Fri-Sun. Snowbird Resort. Contact: Claire Turner, (801) 581-5809.

January 31-February 3—**Pediatric Cardiology** (Sponsor: UUMC). Sun-Wed. Snowbird Resort. Contact: George Veasy, MD, (801) 521-1221.

February 7-12—**Vascular Imaging: Update on Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird Resort. Contact: (801) 581-8188.

February 8-12—**4th Annual Surgical Pathology Ski Retreat** (Sponsor: UUMC). Mon-Fri. Park City Resort. Contact: Karen Rasmussen, (801) 268-7097.

February 8-13—**Family Practice Refresher Course** (Sponsor: UUMC). Mon-Sat. Salt Lake Sheraton. Contact: Kathy Chisholm, (801) 581-8634.

February 8-13—**Utah Ophthalmological Society Annual Winter Meeting** (Sponsor: UOS). Mon-Sat. Little America Hotel, Salt Lake City. 15 hrs. Contact: Carol Leavitt, (801) 355-7477.

February 15-19—**11th Annual Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Mon-Fri. Park City Resort. Contact: M. Beckman, (801) 581-7480.

February 17-20—**29th Annual OB-GYN Update** (Sponsor: UUMC). Wed-Sat. Snowbird Resort. Contact: Sheryl Martin, (801) 581-5501.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital. 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

February 19-23—**33rd Annual Postgrad Course in Anesthesiology** (Sponsor: UUMC). Fri-Tues. Salt Lake City. Contact: Vicky Larsen, (801) 581-6393.

February 21-28—**Intermountain Dermatology Meeting** (Sponsor: UUMC). Sun-Sun. Colorado. Contact: Bernie Lasalle, (801) 581-7837.

February 24-27—**Reproductive Endocrinology and Infertility** (Sponsor: UUMC). Wed-Sat. Snowbird Resort. Contact: Sheryl Martin, (801) 581-5501.

February 24-27—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City. Contact: Amy Eschelman, (801) 521-1221.

February 28-March 4—**Vascular Imaging: Update on Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird Resort. Contact: (801) 581-8188.

February 29-March 4—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. Contact: Jennifer Fossum, (801) 581-3581.

March 7-11—**Gastroenterology Update** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. Contact: Jennifer Fossum, (801) 581-3581.

March 1988—**Nutrition in Contemporary Medicine** (Sponsor: UUMC). Contact: Jennifer Fossum, (801) 581-3581.

March 30-April 1—**Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. Contact: K. Blosch, (801) 466-3500.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

December 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

December 17—**Conjoined Conference: Carcinoma of the Bowel.** Spokane. Thurs. Contact: Jo Ann Lambert. (509) 458-7159.

January 7—**New Concepts in Bronchospastic Disease.** Spokane. Thurs. Contact: Jo Ann Lambert, (509) 458-7159.

January 14—**Conjoined Conference: Childhood Maligencies Recognizing Symptoms.** Spokane. Thurs. Contact: Jo Ann Lambert, (509) 458-7159.

January 20—**Health Effects of Wood Smoke.** Seattle. Wed. Contact: U/W, (206) 543-1069.

January 21—**Conjoined Conference: The Significance of Hematuria.** Spokane. Thurs. Contact: Jo Ann Lambert, (509) 458-7159.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 764)

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ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

SAN FRANCISCO—ONE HOUR. Multispecialty group in a growing community is now accepting applications for positions available in Family Practice and Internal Medicine. First year includes guaranteed salary plus incentive. Excellent benefits including malpractice, life, health and disability insurance. Send CV to Number 51, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WASHINGTON, OREGON. Practice opportunities in urgent care and emergency department settings throughout the northwest. Malpractice provided in most locations. Competitive salaries. Recreational activities abound. Write or call L. Poschman, Northwest Emergency Physicians, 11808 Northup Way, Ste 110, Bellevue, WA 98005; (206) 828-6799.

SOUTH CENTRAL WYOMING. Immediate practice opportunity for BC/BE Urologist. Well-equipped JCAH hospital for a service area of approximately 20,000 population. No state or city income tax. Relocation incentives. Superior hunting, fishing, camping, snowmobiling. Three hours to Colorado ski area, five hours to Jackson Hole. One and one-half hours to the mountains. If interested, please send CV and references to D. Abels, DO, Chairman, Recruiting Committee or Richard Mills, Executive Director, Memorial Hospital of Carbon County, Rawlins, WY 82301; (307) 324-2221.

PHYSICIANS WANTED

ARIZONA POSITION AVAILABLE FOR INTERNAL MEDICINE PHYSICIAN (BE/BC). Busy, established and rapidly growing group practice with two Internal Medicine/Pediatric physicians and one Pediatric/Adolescent physician. Benefits and salary with early partnership available. New office building with radiology, laboratory, and pharmacy; also a new hospital. Send CV to Jean K. Pasell, PO Box 37, Casa Grande, AZ 85222; or call (602) 836-5538 for more information.

NEUROLOGIST. Visalia Medical Clinic, Inc, a 37 physician multispecialty group, is searching for a Neurologist to enter an active practice. Located in the San Joaquin Valley in California and serving a market area of approximately 350,000. Excellent hospital services and facilities. BC/BE. Compensation is incentive oriented with rapid advancement to full partnership. Excellent fringe benefits. Please respond to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

ENDOCRINOLOGIST. Full-time BC/BE Endocrinologist for specialty practice in the metropolitan Phoenix area. Emphasis on all areas of clinical endocrinology, diabetes, and research. Laboratory and diabetes education program. Salary negotiable. Position available immediately. Send CV to Number 63, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PHYSICIAN. Full-time, for a four person family practice, in Fremont, northern California bay area. 250-bed hospital one-half mile away. Opportunity for partnership. Broad scope practice, no OB. Immediate opening. Please send inquiries to Tamara Cheney, MD, c/o The Center Medical Group, 2190 Peralta Blvd, Fremont, CA 94536.

SOUTHERN CALIFORNIA

Enjoy professional challenge and growth with a successful and expanding HMO in southern California CIGNA Healthplans of California is seeking Specialists and Primary Care physicians committed to concepts of prevention and health maintenance to join our facilities in Los Angeles and Orange Counties. We offer an excellent compensation and benefits package including profit sharing. For consideration, please forward CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd, Suite 400-49
Glendale, CA 91203

PHYSICIANS WANTED

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEUROSURGERY. Visalia Medical Clinic has an opening for a BC/BE Neurological Surgeon to enter an immediate and active practice. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens. Two Neurosurgeons presently serving this area. Excellent hospital services and facilities. Must be BC/BE. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

NEVADA—EMERGENCY MEDICINE. An Emergency Department full-time staff position and medical directorship opportunities are currently available at client hospital in Fallon, Nevada, located one hour east of Reno. Full-service community hospital with low-volume Emergency Department. Competitive rate of reimbursement, occurrence malpractice insurance coverage, CME allowance. Director also receives health benefits which include dependents. For more details, contact George Tracy, Spectrum Emergency Care, 6275 Lehman Dr, Ste C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

CALIFORNIA. Emergency Medicine Faculty Positions. Immediate opportunities available for career-oriented Emergency Physicians who possess excellent clinical and teaching skills to join the faculty of Emergency Medicine department. BC in Family Practice, Internal Medicine, Surgery, and/or BE in Emergency Medicine. Our facility, located in southern California, averages 38,000 Emergency Department visits per year, is a level II trauma center, regional burn center and neonatology intensive care center. These positions require a teaching commitment in a university-affiliated Family Practice training program. We offer a competitive remuneration package to include salary, malpractice insurance, time off and flexible scheduling. Send CV to Empire Medical Group, PO Box 3571, San Bernardino, CA 92413.

CENTRAL OREGON community seeks BE/BC Internist. 103-bed combination facility has ICU/CCU. Service area of 12,000. Coverage available by Internal Medicine group in neighboring town. Generous practice assistance package. An outdoorsman's winter and summer paradise! Contact Cynthia Lacro, Prosearch, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070.

BEAUTIFUL COLORADO—Family Practice, Internal Medicine, and Occupational Physicians. Send CV to D. A. Franklin, MD, Medical Director, HealthWatch Medical Centers, 3400 Industrial Lane, Ste A, Broomfield, CO 80020.

SAN FRANCISCO BAY AREA. BE/BC Internist needed immediately to join 20 physician Internal Medicine Department in large private multispecialty group. Preference given to candidates with IM residency at major academic institution. Competitive salary, liberal fringe benefits, and early corporate membership. Send CV or contact Robert H. Prall, MD, San Jose Medical Group, Inc., 45 S. 17th St, San Jose, CA 95112; (408) 282-7833.

NEPHROLOGIST. Full-time BC/BE Nephrologist for specialty practice in the metropolitan Phoenix area. Large acute and chronic dialysis, CAPD, and transplantation patient load. Salary negotiable. Send CV to Number 64, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 764)

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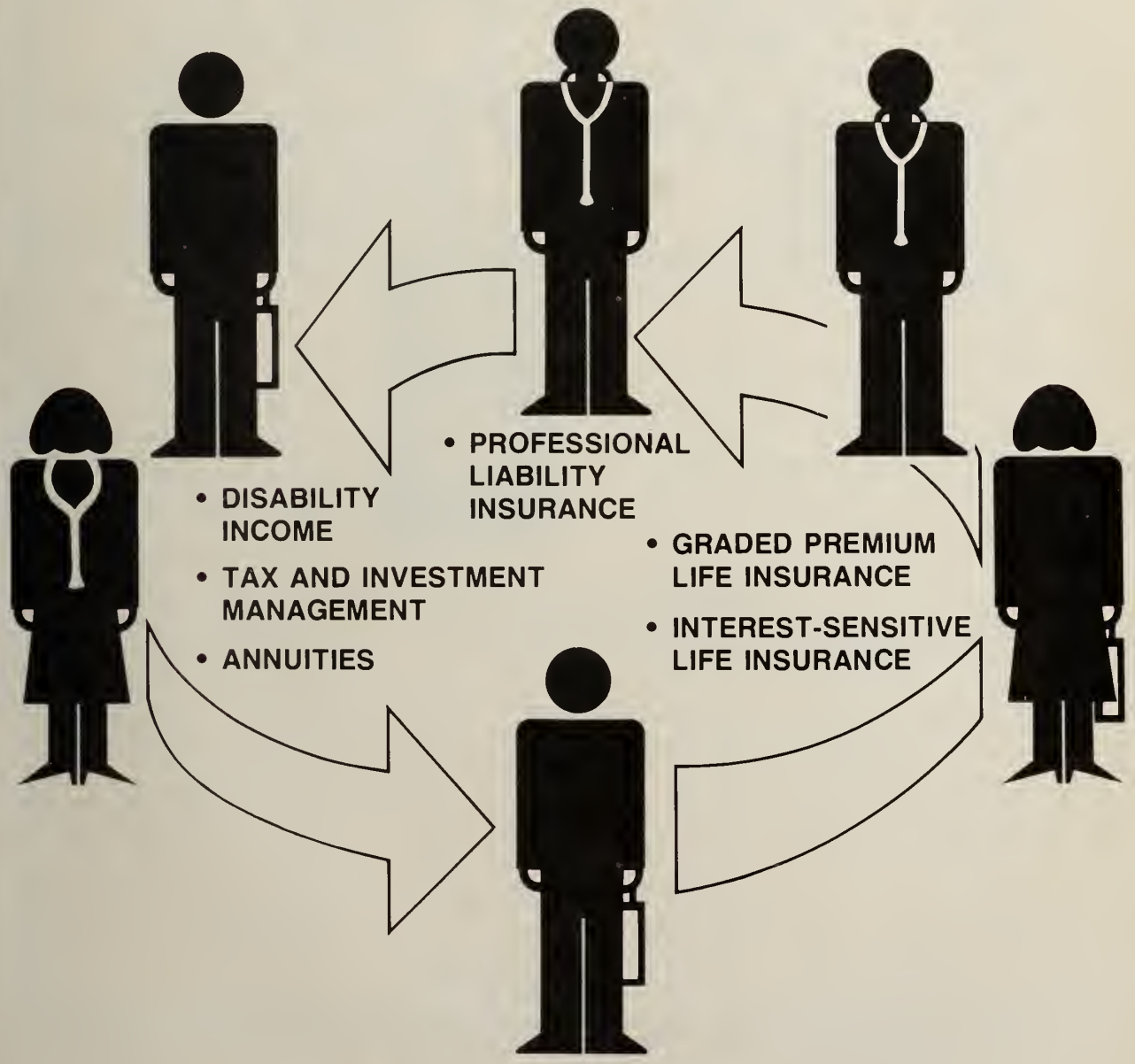

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CONTINUING MEDICAL EDUCATION

(Continued from Page 760)

January 22—**Biliary Tract Diseases—Stones and Tumors.** Seattle. Fri. Contact: VMMC.

January 28—**Conjoined Conference: Diagnosis and Management of Carcinoma of the Breast.** Spokane. Thurs. Contact: Jo Ann Lambert, (509) 458-7159.

January 29-30—**Orbital Problems and Treatment: Plastic and Reconstructive Surgery (WSAO Annual Meeting).** Seattle. Fri-Sat. Contact: Patti Smith, (206) 441-9762.

February 4-5—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: Maria Lilja, (206) 543-1050.

February 5—**Esophageal Disorders in Clinical Practice.** Seattle. Fri. Contact: VMMC.

February 10-13—**Washington State Academy of Physician Assistants CME Conference.** Bellevue. Wed-Sat. Contact: Kory Diemert, (206) 441-9762.

February 19-20—**Medicine for Psychotherapists.** Seattle. Fri-Sat. Contact: VMMC.

February 20-27—**Maternal-Fetal Medicine Update.** Seattle. One week. Contact: U/W.

February 25-26—**Survivorship.** Spokane. Thurs-Fri. Contact: Carolyn Hunter, (509) 325-6146.

March 3-4—**Northwest Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Thurs-Fri. Contact: William Lassey, (509) 747-1012.

March 4-5—**Primary Care of Orthopaedics.** Seattle. Fri-Sat. Contact: Maria Lilja, (206) 543-1050.

March 4-5—**Soft Tissue Surgery.** Seattle. Fri-Sat. Contact: VMMC.

March 11—**Recent Developments in Occupational Medicine.** Fri. Contact: U/W, (206) 543-1069.

March 15—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Patti Smith, (206) 441-9762.

(Continued on Page 769)

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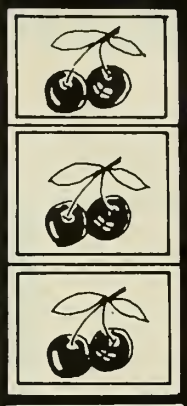

CLASSIFIED INFO (415) 863-5522 EXT 244

(Continued from Page 762)

PHYSICIANS WANTED

INTERNIST BC/BE to assume busy established practice. Share call with three other Internists. Excellent hospital and family oriented community. University affiliation possible. Send CV to Search Committee, PO Box 1564, Redlands, CA 92373.

BROOKINGS, OREGON. Evening and weekend clinic. Family practice or emergency experience preferred. $35 per hour. Send CV to Art B. Wong, MD, FACEP, Emergency Physicians' Medical Group, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

VANCOUVER, WASHINGTON. BC/BE Family Practitioner, Gastroenterologist and General Internist to join a growing, well-established, 40 physician multispecialty group. Clinic is in a high growth area with a multitude of outstanding recreational, cultural and educational opportunities in nearby Portland, Oregon, Mt. Hood and the Columbia Gorge. High-quality practice with excellent vacation and benefits package. Salary first two years, with potential for full partnership. Send CV to Roger R. Garretson, 700 N.E. 87th Ave, Vancouver, WA 98664.

PHYSICIAN/MEDICAL DIRECTOR. Full-time Family Practice physician needed for a community/migrant health center. Experience in medical administration as well as clinical experience helpful. BE or BC with Texas licensure preferred. Emphasis is on comprehensive ambulatory care, including OB care. Hospital inpatient care of registered patients required. The facility is located in a very pleasant rural community 85 miles southwest of San Antonio, Texas. Very competitive salary. Send CV or résumé with references to Rachel A. Gonzales, Executive Director, Uvalde County Clinic, Inc., 1009 Garnerfield Rd., Uvalde, TX 78801.

PHYSICIANS WANTED

INTERNIST WANTED to join five physician BC Internal Medicine group. Desirable San Francisco bay area community. Please reply to Number 75, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE PHYSICIAN. Southern California, Los Angeles suburb. BC/BE FP desired for group practice. Join five residency trained FPs in comprehensive practice. OB optional. Excellent hospital and support services. Salary, production, and benefits commensurate with experience. Malpractice paid. Send CV or call Mr Ed Myatt, Executive Director, Northridge Community Medical Group, 8330 Reseda Blvd., Northridge, CA 91324; (818) 886-1376.

GASTROENTEROLOGIST BC/BE to be a second Gastroenterologist in a 36 physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package with excellent recreational, cultural, and educational opportunities. Send CV to Search Committee, Walla Walla Clinic, 55 West Tietan, Walla Walla, WA 99362.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

TUCSON, ARIZONA. Family Practice, Internal Medicine, Urgent Care. CIGNA Healthplan has career opportunities in Tucson, Arizona. Professional liability coverage, paid vacations, CME, pension, and retirement benefits are provided. Please submit CV to Director or Physician Recruitment, CIGNA Healthplan of Arizona, Inc., 4907 E. Broadway, Ste 100, Tucson, AZ 85711; (602) 571-6517. Equal Opportunity Employer, M/F/H/V.

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NEUROSURGEON. EXPERIENCED BC PHYSICIAN to join established office adjacent to regional trauma center in northern California college town. Send CV to Number 69, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN FRANCISCO BAY AREA multispecialty group seeks Gastroenterologist, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

CALIFORNIA, SAN FRANCISCO, SUBURBAN. Family Practice or Emergency Medicine physician to join group of five FP/EM MDs. $60,000 plus bonus to start. Four and one-half days per week and every fifth weekend. No OB; hospital care optional. Write G. N. Rogan, MD, 1482 Reliez Valley Rd, Lafayette, CA 94549, Immediate need.

GENERAL SURGEON—BE/BC. Outstanding opportunity for aggressive surgeon with a highly profitable, well-established, fee-for-service, multispecialty clinic. 14 physicians on staff. Ready made practice. Unmatchable guaranteed salary first year, then ownership. New hospital. Wonderful family town with nationally recognized school system and unequalled outdoor recreation possibilities. Telephone calls will not be accepted. Send CV to John Brust, Mesaba Clinic, 1814 14th Ave East, Hibbing, MN 55746.

NEW MEXICO. BC/BE Primary Care Physician for 500-bed psychiatric/geriatric hospital. Exciting programs in an exciting location, with superb climate, recreational and cultural benefits. Base salary $70,017 plus optional on-call salary supplement to $10,000. Fringe benefits are 21%, including paid malpractice and license fees, 2.5% per year retirement. Contact Philip Taulbee, MD, Medical Director, Las Vegas Medical Center, Box 1388, Las Vegas, NM 87701; (505) 425-6711.

SAN FRANCISCO BAY AREA multispecialty group seeks Neurologist, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

UROLOGIST BC/BE. To be 2nd Urologist in a 36 physician multispecialty clinic. Guaranteed salary and immediate full participation in incentive program. Excellent benefit package and excellent recreational, cultural and educational opportunities. Send CV to Search Committee, 55 W. Tietan, Walla Walla, WA 99362.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

(Continued on Page 766)

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AIR FORCE

(Continued from Page 764)

OCCUPATIONAL/FAMILY PRACTICE. Excellent opportunities with the west coast's leading provider of Occupational/Family Practice medicine. Full-time/part-time positions throughout California and Washington (Seattle/Tacoma). Current license/CPR. Prior outpatient/family practice/industrial-type trauma experience. Attractive salary/incentives/benefits/malpractice. Contact Personnel Director, ReadiCare, Inc., 446 Oakmead Parkway, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

PARTNER DESIRED—BC/BE Radiologist to share hospital and office practice. Must enjoy general radiology, mammography, nuclear medicine, ultrasound and CT. Hands on experience in real time ultrasound helpful. Excellent salary and benefits. Early partnership. Will consider longer term locums. Send CV to Radiology, 5681 N. Fresno St, Fresno, CA 93710.

SAN FRANCISCO BAY AREA multispecialty group seeks Family Practitioner, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

ORTHOPEDIST. The west coast's leading Occupational/Family Practice medical provider has full-time/part-time opportunities for Orthopedic Specialist in California and Washington (Seattle/Tacoma). Attractive package includes: guaranteed salary, incentive bonus and benefits. Current license. Contact Personnel Director, ReadiCare, Inc., 446 Oakmead Parkway, Sunnyvale, CA 94086; (800) 237-3234. Join our dynamic team of professionals. Practice and live in an incomparable environment.

OREGON—FAMILY PRACTITIONERS, INTERNISTS, PEDIATRICIANS. Private practice opportunities are immediately available in beautiful northwest Oregon. Call today to investigate this opportunity to practice challenging medicine in a hospital-supported surrounding, while enjoying an incomparable lifestyle in one of the Northwest's most scenic areas. Competitive first year guarantees offered to the selected candidate. Interview and relocation expenses absorbed by the client. For complete details, contact Jim Murphy, Spectrum Search, PO Box 27352, St. Louis, MO 63141; 1 (800) 237-6906; (314) 878-2280.

CHAIRMAN, DEPARTMENT OF INTERNAL MEDICINE, KERN MEDICAL CENTER. A county operated teaching hospital is seeking a chairman for this UCLA affiliated department. The department has nine full-time and part-time members, 18 residency positions all currently filled with quality graduates. Qualifications: BC in Internal Medicine, established record of scholarly achievement in teaching and patient care, demonstrated management skills to direct a fully accredited residency program in an active public hospital and relate to other programs at Kern Medical Center and the UCLA system. Candidate must be eligible for appointment to senior faculty position at UCLA and be licensed in the State of California. (The County of Kern is an Equal Opportunity Employer.) Address inquiries with CV to Paul Toot, MD, Chairman, Internal Medicine Search Committee, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

NEW MEXICO—FAMILY PHYSICIAN. Innovative practice in New Mexico mountain community needs third BC/BE FP. Salary guarantee with reasonable work schedule. Video available showing our practice style, area, and people. Gila Family Care, 1121 West St, Silver City, NM 88061.

INTERNIST, BC, to join four others in a busy practice in pleasant Sierra foothills community. Abundant recreational opportunities, yet near urban centers. Contact Dennis Nousaine, MD, FACP, 815 Court St, Ste 7, Jackson, CA 95642.

PART-TIME MEDICAL CONSULTANT CONTRACTS

Physicians needed to work under contract, on a part-time basis for the Social Security Administration's Disability Insurance Program, involves review of medical evidence in disability claims at 100 Van Ness Ave, San Francisco, California. No patient contact. Applicants must: (1) have a valid license to practice medicine in the US; (2) have current or recent clinical experience; and (3) be available between 7:00 am and 5:30 pm, Monday through Friday for case review. Subject to change, the specialties needed are Orthopedics, Physiatry and Internal Medicine. Women and minorities are encouraged to apply. If interested in applying, please submit a letter of interest or call Perlena Turner at (415) 556-8852 by December 23, 1987 (collect calls are not accepted).

MAIL TO: Contracting Officer
Department of Health and Human Services
50 United Nations Plaza, Room 403
San Francisco, CA 94102

THE COMMUNITY OF ARTESIA, NEW MEXICO is seeking a BC/BE General Surgeon to establish a private practice. Fully-equipped office with established referral patterns available for purchase. Community-based financial assistance may be available to the right individual. Artesia is a community of 14,000 located in southeast New Mexico. A great place to raise a family—peaceful community with year 'round recreation and excellent weather. Fully-equipped, 38-bed new hospital. Please submit CV to Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, ext. 8300.

FAMILY PRACTITIONER. Tulare County is seeking a BE/BC Family Practitioner to practice in an out-patient clinic which includes inpatient duties, with 14 physicians. Ability to perform simple OB required. The County provides a benefit package which includes malpractice insurance coverage. Consider a semi-rural lifestyle with cultural amenities of metropolitan areas easily accessed and Kings Canyon and Sequoia National Park nearby. Salary $89,724-$94,296 annually. Send CV to Tulare County Personnel, 2900 W. Burrel, Visalia, CA 93291, (209) 733-6266; Equal Opportunity Employer.

FAMILY PRACTITIONER. Visalia Medical Clinic has an opening for a BC/BE Family Practitioner to join a four-physician department. Located in the San Joaquin Valley of California, serving a market area of approximately 350,000 citizens, the Visalia Medical Clinic is a 40 physician multispecialty clinic. Excellent hospital services and facilities. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

EUGENE, OREGON. Well-established, eight physician Family Practice group is seeking BC/BE Family Physician with interest in OB. Anticipate partnership after one year. Exceptional cultural and recreational opportunities. Home of University of Oregon. Please send CV to Rob Daugherty, MD, or Kendall Hills, MD, River Road Medical Group, 2400 River Rd, Eugene OR 97404, or call (503) 688-7527.

INTERNISTS. MED Group operates a growing suburban Sacramento area network of successful ambulatory care centers. We seek several talented, personable BE/BC Internists to develop and maintain traditional IM practices at each of our centers from the many patient referrals we generate. Compensation package includes a salary guarantee ($80,000), revenue sharing, malpractice insurance, vacation, CME stipends and other benefits. Contact Daniel Newman, MD, MED Group, 3441 Arden Way, Sacramento, CA 95825; (916) 487-7777.

UTAH. Full-time physicians needed for urgent care centers in Ogden area. Send CV to Val Rollins, MD, Emergency Department, St. Benedicts Hospital, 5475 S. 500 East, Ogden, UT 84405; or call (801) 479-2376.

URGENT CARE/INTERNAL MEDICINE/ENDOCRINOLOGY/PEDIATRICS physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing southwest community (population 500,000 plus). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics/Internal Medicine/Subspecialties/24-hour Urgent Care. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with CV to Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645.

THE PERFECT PARTNERSHIP. We handle the business. You practice medicine. And we both prosper. MED Group is a growing Sacramento and Ventura County area network of sophisticated convenient emergency and family medical care centers. We have full-time and part-time openings for talented, personable physicians who can build practices by providing top-quality medical care. BC in IM, FP or EM is preferred. Some of the outstanding MED Group benefits include directorship opportunities, flexible scheduling with no overnight call, an updated compensation plan featuring attractive salaries ($75,000-$105,000 annually for 45-hour weeks), guaranteed profit sharing, equity participation through annual stock option grants, health insurance coverage, two weeks paid vacation, paid malpractice insurance, CME stipends, franchise-model practice ownership plans and more. For additional information, please call or send your CV in confidence to Charles Pietrafesa, MD, MED Group, 12327 Santa Monica Blvd, Los Angeles, CA 90025; (213) 826-1805.

RESEARCH ASSOCIATE—GASTROENTEROLOGY. Research industrial work health hazards including asbestos research. Collect and analyze data on workers exposed to hazardous materials. Evaluate cases, advise, and consult with administration and physicians regarding treatment. Research development of diagnostic and treatment procedures. Requires doctorate in Gastroenterology and four years experience same or four years Gastroenterological research experience. $3,920 per month. Job site and interview: Long Beach, California. Send resume to Job #MA11523, PO Box 9560, Sacramento, CA 95823-0560 no later than January 11, 1988.

MARIN COUNTY, CALIFORNIA, ORTHOPEDIC SURGEON to join established growing, multispecialty group. BC/BE required. This group of 55 plus physicians provides care to both fee-for-service and prepaid patients. Excellent practice opportunity and superb living conditions. Guaranteed starting salary with ownership potential. Send CV to RVMC, Inc., 1350 S. Eliseo Dr, Greenbrae, CA 94904, Attn: Personnel.

INTERNIST NEEDED FULL-TIME. Primary Care position for Board certified Internist is now available with a growing San Francisco Health Plan. The position includes both inpatient and outpatient responsibilities. Send CV to Medical Director, French Health Plan, 4131 Geary Blvd, San Francisco, CA 94118.

(Continued on Page 767)

Nevada Academy of Family Physicians 20th Anniversary

WINTER ASSEMBLY

January 31–February 5, 1988
Caesars Tahoe Hotel—Stateline, Nevada
Chairman: Richard C. Inskip, MD, AAFP Past President

The "original and still the best" CME/SKI meeting in the West!

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- Nastar-sanctioned races; trophies and prizes
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- Racquetball tournament; trophies awarded
- Spouse program
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  (Indoor pool, health club/spa, entertainment and gaming, covered parking, child care)

Registration fee: $400 Practicing Physicians
$300 Residents, Retirees, Nurses, PAs

Includes all scientific sessions, breakfasts, coffee breaks, spouse program, plus admission for 2 adults to all evening social events and awards banquet.

For more information call or write:

NEVADA ACADEMY OF FAMILY PHYSICIANS
P.O. Box 7471 • Reno, NV 89510 • 702/826-5100

(Continued from Page 766)

PHYSICIANS WANTED

INTERNAL MEDICINE—CENTRAL UTAH. Seeking General Internist and/or Internist with subspecialty in Endocrinology or Infectious Disease to join established Internal Medicine clinic. 350-bed hospital across the street. First year salary with possible partnership after first year. Inquire: Dorothy Farnworth, Central Utah Medical Clinic, 1055 North 500 West, Provo, UT 84601.

EMERGENCY MEDICINE. We are an established 35 physician partnership in northern California and we are seeking BE/BC Emergency Physicians to join us. All of our facilities have moderate volumes, many serve as EMS base stations. Salary and benefits are competitive; malpractice is paid. If interested in a career in Emergency Medicine with us, please contact Sacramento Emergency Medical Group, 4325 Auburn Blvd, Ste 100, Sacramento, CA 95841.

PHYSICIANS WANTED

THE IRVINE MEDICAL CENTER AND THE UNIVERSITY OF CALIFORNIA-IRVINE, DEPARTMENT OF RADIOLOGICAL SCIENCES are seeking a full-time faculty member for the Department of Radiological Sciences at the Clinical Associate Professor or Clinical Professor level who would be assigned as Director of the Department of Radiology at Irvine Medical Center. The Irvine Medical Center is a new 177-bed hospital currently under construction in Irvine, California. Hospital opening is scheduled for fall of 1988. Administrative experience and academic background, including teaching and/or research, is required. Please send CV and the names of five references to Richard M. Friedenberg, MD, Professor and Chairman, Department of Radiological Sciences, University of California, Irvine, 101 City Drive South, Orange, CA 92668. The University of California is an Affirmative Action and an Equal Opportunity Employer.

PHYSICIANS WANTED

SOUTHERN CALIFORNIA COASTAL COMMUNITY, FP/IM physicians with acute care skills needed to join primary care/ambulatory care practice. State-of-the-art hospital affiliated facilities located in highly desirable areas. Fee-for-service with administrative opportunities and early partnership status. Contact J. Lewis, MD, Executive Director, (714) 891-9008 or (213) 618-9200.

INTERNAL MEDICINE. Full-time position for a BC/BE Internist in a 15 resident, seven faculty, rural Family Medicine program affiliated with the University of California, Davis. Duties will include supervising residents on the medical ward and in the ICU/CCU areas. Excellent salary. Send inquiries with CV to E. Hughell, MD, Director, Family Practice Residency Program, Merced Community Medical Center, PO Box 231, Merced, CA 95340; (209) 385-7172. EOE

(Continued on Page 768)

(Continued from Page 767)

PHYSICIANS WANTED

WASHINGTON STATE

Growing Puget Sound Community

Leading multispecialty group of 14 to add:

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- GENERAL SURGEON
- ORTHOPEDIST
- NEUROLOGIST
- OB/GYN

Private practice option. Share expenses with well-structured group. Twenty minutes to 230-bed hospital. Female and male applicants encouraged. Young population, waterfront setting. One hour to Seattle.

The Friedrich Group, Inc.
9284 Ferncliff Northeast
Bainbridge Island, WA 98110
(206) 547-7850 or (206) 842-5248

OB/GYN, CALIFORNIA, CENTRAL SAN JOAQUIN VALLEY. County sponsored, sixteen (16) physician multispecialty group practice with three (3) satellite locations is looking for a BC/BE OB/GYN to provide ambulatory, delivery, and surgical services. Committed to high quality care. The position provides a comprehensive benefit package and includes malpractice insurance coverage. Consider a semirural life-style with cultural amenities and easy access to metropolitan areas, the Sierra Nevada Mountains, and the Pacific Ocean. Salary $98,112-$103,116 annually. Send CV to Michael L. MacLean, MD, Hillman Health Center, 1062 South "K" St, Tulare, CA 93274; (209) 688-2015. Equal Opportunity Employer.

CALIFORNIA, SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for high volume Emergency department. Emergency Medicine BC/BE mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation, one week CME, paid malpractice, health and life insurance, corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd, Hayward, CA 94545.

CHIEF RESIDENT AND RII OR III POSITIONS. The University of Nevada School of Medicine is seeking a Chief Resident and several RII or RIII positions with the Department of Internal Medicine. Must be eligible for licensure in Nevada. Salary dependent upon qualifications. Send letter of application and two reference letters to Roger K. Ferguson, MD, Chairman, Department of Medicine, University of Nevada School of Medicine, Reno, NV 89557; or call (702) 784-6171. This position will remain open until filled. AA/EOE.

HEALTHTRUST, INC. owns 19 state-of-the-art facilities in many lovely suburban and rural communities throughout the western medical association region which have a variety of solo, group, and associate private practice opportunities for the following BE/BC physicians: Physiatrist, Family Practitioner, Internist, Pulmonologist, Cardiologist, Cardiosurgeon, Neurosurgeon, Neurologist, Psychiatrist, OB/GYN, Pediatrician, Pathologist, General Surgeon, Oncologist, Orthopedic Surgeon, Radiologist, Otolaryngologist, Urologist, Emergency Physician, Neonatologist, Gastroenterologist. Let us help you explore a practice opportunity in a community that's just right for you. No cost or obligation associated with any inquiry. For more information, send your CV to Kay Cox or Terry Moran, HealthTrust, Inc., 4525 Harding Road, Nashville, TN 37205, or call 1-800-NASH-HTI/(615) 383-4444 (collect).

PHYSICIANS WANTED

TUOLUMNE. Sierra Foothills, Yosemite area—base station hospital with 12,000 visits per year. Openings for experienced Emergency Room MDs. Outstanding mountain, recreation area in the heart of California gold country. Fee-for-service approximately $40 per hour or greater. Please send CV to Art B. Wong, MD, FACEP, Emergency Physicians' Medical Group, 1 Maritime Plaza, Ste 710, San Francisco, CA 94111.

CARDIOLOGIST, BC/BE. Invasive Cardiologist with PTCA skills to join two FACC Cardiologists in expanding ten physician Internal Medicine group in San Diego. Position available July 1988 or sooner. Reply with CV, statement of interest, and three letters of reference, to F. C. Millward, Administrator, 5111 Garfield St, La Mesa, CA 92041.

INTERNIST. To join two Primary Care Internists in private practice in beautiful far-northern California one hour below major center. Midway between Portland and San Francisco, we have a rural setting with sophisticated practice and excellent hospital facilities. Subspecialty interest desirable within primary care framework. Salary and benefits with partnership an early goal. CV and your interests to R. H. Alley, Jr, MD, 105 Oberlin Rd, Yreka, CA 96097.

CALIFORNIA. BE/BC Internist to join staff of eight Internists in 15 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to David A. Hellstern, Administrator, Kaweah Medical Group, Inc., 222 W. Willow, Visalia, CA 93291.

OB/GYN. Tulare County is looking for a BC/BE OB/GYN to practice in an outpatient clinic, which includes inpatient duties, with 14 physicians. The county provides a benefit package which includes malpractice insurance coverage. Consider a semirural life-style with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $98,112-$103,116 annually. Send CV to: Tulare County Personnel, 2900 W. Burrel, Visalia, CA 93291; (209) 733-6266. Equal Opportunity Employer.

BC/BE CARDIOLOGIST. To join three invasive/noninvasive Cardiologists in practice, Portland, Oregon metropolitan area. Send CV to Number 76, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SAN FRANCISCO. One hour west, growing multispecialty group needs Family Practitioner, Internist, Urgent Care, Urologist, Pediatrician, Orthopedist, ENT, Psychiatrist, Cardiologist. Good salary, benefits, incentive, early partnership. Write: Annette Pombo, Eaton Medical Group, 445 W. Eaton, Tracy, CA 95376; (209) 835-0264.

OCCUPATIONAL MEDICINE PHYSICIAN. The Virginia Mason Clinic is seeking a physician to join an expanding occupational medicine clinic system within a major medical center. The position requires experience with minor trauma and injury care. Standard clinic hours, but flexibility a must. Applicant must have a Washington State license or be license eligible; BC/BE in Occupational Medicine or Emergency Medicine preferred. The Virginia Mason Medical Center is a tertiary health care system serving the pacific northwest region. The Medical Center consists of a 220 physician multispecialty group practice, a 300-bed hospital, twelve satellite clinics, and a research center. Send CV and letter describing background and interest to Linda Hunter, Virginia Mason Clinic, 1100 Ninth Ave, PO Box 900, Seattle, WA 98111.

FAMILY PRACTITIONER. Redwood country on Pacific Ocean. University town. Prefer female and cesarean section competent. Full- or part-time. Family Practice nonprofit clinic with accent on women's and children's health care. Staffed by two OB competent Family Practitioners, one General Practitioner (practicing only women's health), two Pediatricians, and four PAs. Contact: Donald Verwayen, Administrator, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

PHYSICIANS WANTED

ONCOLOGIST/INTERNIST. BC/BE to join 21 physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

GASTROENTEROLOGIST. 55 physician multispecialty medical group seeks full-time BC/BE Gastroenterologist. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004.

CALIFORNIA. BC/BE Pediatrician to join staff of three Pediatricians in 15 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to David A. Hellstern, Administrator, Kaweah Medical Group, Inc., 222 W. Willow St, Visalia, CA 93291.

ESTABLISHED BC FAMILY PRACTITIONER in south central Washington seeks BE/BC associate with OB interest. Practice in rural, family-oriented community serving area of 45,000. Income guarantee and assistance with relocation. Ski at White Pass. Fishing and other water sports on nearby Rimrock Lake and Columbia River. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

BE/BC FAMILY PRACTICE physician wanted to join young successful BC Family Practitioner to start new group in northeastern Colorado community. Includes OB. Service area of 25,000. Generous first year income guarantee and assistance with relocation. Only one and one-half hours from Denver. Contact PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (503) 256-2070, ext 202.

PACIFIC NORTHWEST, NEAR EUGENE, OREGON. BE/BC Internist wanted to join Family Practitioner group. Share call with Internists. Minimum salary guarantee. Good schools/outdoor recreation; University of Oregon/cultural events within 30 minutes. Contact John Hoopes, Cottage Grove Hospital, 1340 Birch St, Cottage Grove, OR 97424; (503) 942-0511.

IDAHO. Family Practitioner with interest in OB wanted to join three Family Practitioners serving scenic northern Idaho community. Hospital provides complete assistance—office, salary, full benefits. BE/BC and cesarean section experience required. Enjoy outdoor recreation, rural life-style. Contact Jean Erickson, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220-4199; (503) 256-2070.

SAN FRANCISCO BAY AREA multispecialty group seeks Internist, BC/BE, to join 26 congenial men and women delivering quality care in a combined fee-for-service, HMO/PPO setting. Bay Valley Medical Group, Attn: Don Lass, 27212 Calaroga Ave, Hayward, CA 94545; (415) 785-5000.

FAMILY PRACTICE/GENERAL PRACTICE wanted for full-time practice to work three days a week and share with another practitioner. Rural setting, good pay, nice people. Can commute for two nights a week, one hour—Sacramento, one hour and 15 minutes—Nevada City, two hours—San Francisco. Contact Charles Rath, MD, 199 E Webster St, Colusa, CA 95932; (916) 458-7739.

CALIFORNIA—NORTH SAN FRANCISCO BAY AREA. Excellent opportunity for BC/BE Family Practitioner to join growing department. Flexible starting date. Multispecialty clinic emphasizing personalized care. Full hospital privileges including ICU/CCU. No obstetrics. Very favorable call schedule. Prepaid HMO practice provides excellent salary, benefits. Forward CV to Steven Freedman, MD, Kaiser Permanente, 1550 Gateway Blvd, Fairfield, CA 94533; (707) 427-4260.

(Continued on Page 770)

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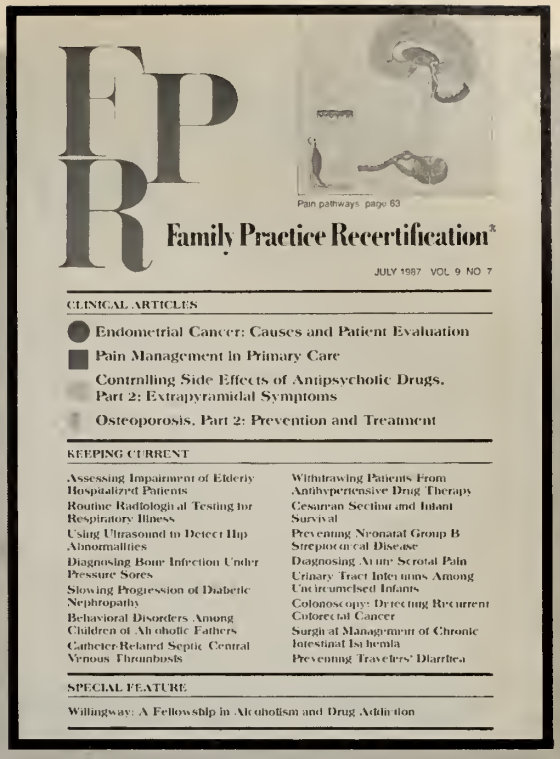
FPR
Pain pathways page 63
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JULY 1987 VOL 9 NO 7
CLINICAL ARTICLES
Endometrial Cancer: Causes and Patient Evaluation
Pain Management in Primary Care
Controlling Side Effects of Antipsychotic Drugs, Part 2: Extrapyramidal Symptoms
Osteoporosis, Part 2: Prevention and Treatment
KEEPING CURRENT
Assessing Impairment of Elderly Hospitalized Patients
Routine Radiological Testing for Respiratory Illness
Using Ultrasound to Detect Hip Abnormalities
Diagnosing Bone Infection Under Pressure Sores
Slowing Progression of Diabetic Nephropathy
Behavioral Disorders Among Children of Alcoholic Fathers
Catheter-Related Septic Central Venous Thrombosis
Withdrawing Patients From Antihypertensive Drug Therapy
Cesarean Section and Infant Survival
Preventing Neonatal Group B Streptococcal Disease
Diagnosing Acute Scrotal Pain
Urinary Tract Infections Among Uncircumcised Infants
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Willingway: A Fellowship in Alcoholism and Drug Addiction

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CONTINUING MEDICAL EDUCATION

March 18-19—**NW Regional Rural Health Conference. Rural Health: Strategies and Solutions.** Spokane. Fri-Sat. Contact: ICNE, (509) 325-6146.

March 19-23—**11th Annual Physical Medicine and Rehabilitation Review.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 19-23—**Death Investigation.** Seattle. Sat-Wed. Contact: Maria Lilja, (206) 543-1050.

March 23-25—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: U/W, (206) 543-1069.

March 25—**Update in Contrast Media: An Evening of Uroradiology.** Seattle. Fri. Contact: VMMC.

April 19—**Washington State Academy of Ophthalmology Monthly Meeting.** TBA. Tues. Contact: Pattie Smith, (206) 441-9762.

May 5-6—**Health Effects of Synthetic Fibers.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

May 13—**Current Drug Topics—Pharmacology for the Practitioner.** Seattle. Fri. Contact: VMMC.

May 19-20—**Travel and Medicine.** Seattle. Thurs-Fri. Contact: Maria Lilja, (206) 543-1050.

May 19-21—**Emergency Medicine Update.** Seattle. Thurs-Sat. Contact: VMMC.

WYOMING

February 28-March 6—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Jackson Hole. One week. 24 hrs. Contact: Kathy Rairigh, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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ADVANCES IN INTERNAL MEDICINE
$300 fee, CME Credit Offered

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4R118 Medical Center
50 North Medical Drive
Salt Lake City, UT 84132
(801) 581-3581

PARK CITY CONFERENCE

February 15-19, 1988
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Information/Registration: Jonell Murray
HPER-N 239
University of Utah
Salt Lake City, UT 84112
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Major Patty Shackleton, MSC 415-751-1616

(Continued from Page 768)

EMERGENCY MEDICINE UNIVERSITY POSITION

The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine is undergoing rapid academic development, including the creation of an approved residency training program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is an EMT-II Base Station and Training Center and, in addition, provides medical direction for the Hospital's Helicopter Program. Candidates must be BC/BE in Emergency Medicine, and be eligible for licensure in California. Candidates should have proven teaching ability and clinical research experience. A letter outlining teaching background, interests, experience, and research, in addition to a CV, and the names of five references should be sent to:

Robert W. Derlet, MD
Chair of Emergency Medicine Search Committee, Tr. 1219
University of California, Davis, Medical Center
2315 Stockton Blvd
Sacramento, CA 95817

This position will be open until filled; however, applications will not be accepted after June 30, 1988. The University of California is an Affirmative Action/Equal Opportunity Employer.

THE MISSION PARK CLINIC, SOUTHERN CALIFORNIA. The Mission Park Clinic is seeking BC/BE Internist to join a 30 physician multispecialty practice in the north coastal area of San Diego County. Reply with CV, letter of reference and compensation requirements to Donna Mills, Administrator, The Mission Park Clinic, 2201 Mission Ave, Oceanside, CA 92054.

THE VA MEDICAL CENTER, PRESCOTT, ARIZONA is recruiting for a diagnostic Radiologist with ultrasound and Nuclear Medicine training for an active outpatient/inpatient medical service. It is negotiable as to full-time or part-time. The Medical Center is a 200-bed general medical and surgical facility with a staff of approximately 500 employees. It is situated on the grounds of historic Fort Whipple. Prescott is a community of 25,000 set in the Ponderosa pine foothills of the Bradshaw range of the Rocky Mountains. At an elevation of 5,400 feet, the climate is temperate with occasional overnight snows in winter. Daytime temperature average between October and March is 58 degrees. Summer highs are in the 90s. Outdoor recreation and sports abound, year 'round tennis and golf, 100 miles to big mountain skiing. Fishing, sailing, boating on beautiful Lake Mead and Lake Powell. 200 miles to the excitement and night life of Las Vegas. All this in a quiet tree-lined community with 54 churches, a full service regional medical center, three colleges, six libraries, an excellent school system, a negligible crime rate, no pollution, low taxes, and reasonable housing prices. If you are interested in joining us in this idyllic lifestyle and possess the requisite skill and an absolutely spotless professional or employment history, send CV to Chief, Radiology Service (114), VA Medical Center, Prescott, AZ 86313 or call (602) 445-4860, ext 214. We are an Equal Opportunity Employer.

NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

FAMILY PRACTICE PHYSICIAN for busy primary care community clinic in the south bay area. No nights, weekends or on-call. BC/BE Spanish speaking preferred. Graduating residents encouraged to apply. Send CV to Gardner Health Center, 195 E. Virginia St, San Jose, CA 95110 or call Norma Ruiz at (408) 998-2264. EOE.

FAMILY PRACTICE. San Diego. Primary care FP/IM wanted for busy community health center. Spanish speaking preferred. Send résumé to LHFHC, 1809 National Ave, San Diego, CA 92113 or contact Bea Romo (619) 234-8171.

BC/BE NEUROLOGIST to join progressive San Francisco bay area HMO. Busy clinical practice in desirable Marin County. Competitive income and excellent benefits. EEG experience necessary/EMG expertise helpful. Position will be available July 1988. Please contact Jonathan Freudman, MD, Assistant Chief, Department of Internal Medicine, The Permanente Medical Group, 99 Montecillo Rd, San Rafael, CA 94903. AA/EOE.

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(Continued on Page 774)

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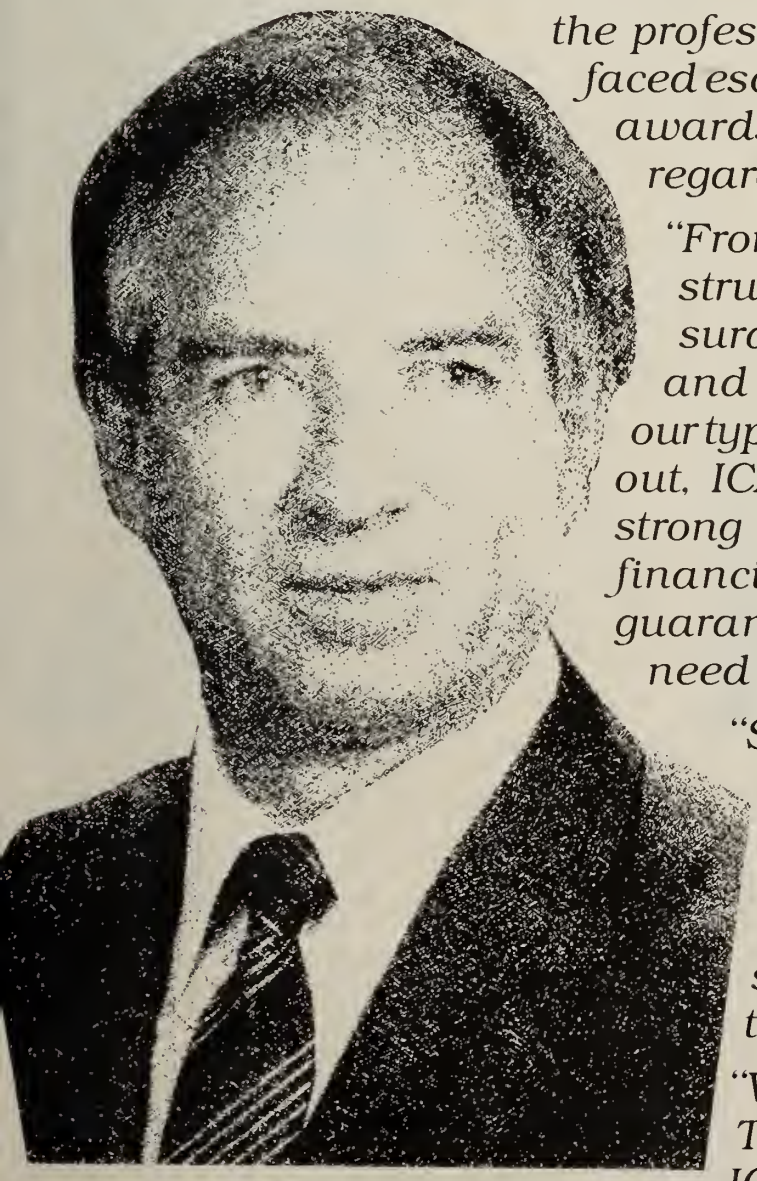

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8:45 AM Introductions
Meade O. Davis, III, MD
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(Participants may select *one* session in each time period—session locations will be announced)

9:00-9:50 AM **SESSION I**
Retirement Planning Under the New Tax Law

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10:00-10:45 AM **SESSION I**
All That Glitters: Investing in Gold and Precious Metals

SESSION II
Strategies for the Conservative Investor

10:45 AM Coffee Break

11:00 AM-12:00 NOON **SESSION I**
How to Invest in Stocks

SESSION II
Whatever Happened to Ginnie Mae?: U.S. Government Guaranteed Investments

12:00 NOON WMS-WMS Auxiliary Luncheon

AFTERNOON SESSION BY ROCKY MOUNTAIN PROFESSIONAL CONSULTANTS, INC.

2:00-3:00 PM *How to Prepare a Practice for Retirement*

3:00 PM Coffee Break

3:15-4:00 PM *Office Efficiency Self-Evaluation*

4:00-5:00 PM *Are You Cheating Yourself on Third Party Reimbursement?*

6:00-8:00 PM President's Reception
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SATURDAY, JANUARY 30, 1988

8:45 AM Welcome
Meade O. Davis, III, MD
WMS President

SATURDAY SESSION BY ROCKY MOUNTAIN PROFESSIONAL CONSULTANTS, INC.

9:00-10:10 AM *To Automate or Not to Automate—That Is the Question*

10:10 AM Coffee Break

10:30-11:30 AM *Potpourri of Personnel Principles (A Primer on Hiring and Motivating Employees)*

11:30 AM-12:15 PM *Everything You Always Wanted to Know About Practice Management But Were Afraid to Ask*
(A question and answer session on all of the morning's topics)

AUXILIARY

FRIDAY, JANUARY 29, 1988

9:00 AM Auxiliary Board Meeting

9:30 AM General Membership Meeting

12:00 NOON WMS-WMS Auxiliary Luncheon

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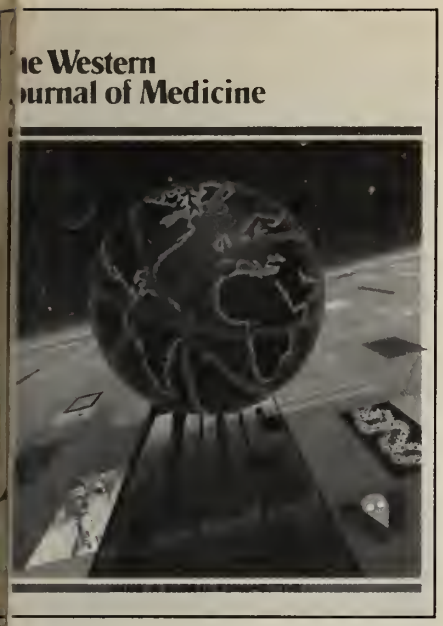

AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director, Special Programme on AIDS
World Health Organization, Geneva

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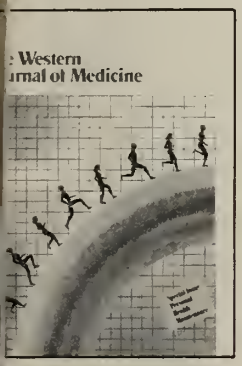

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—John H. Holbrook, MD

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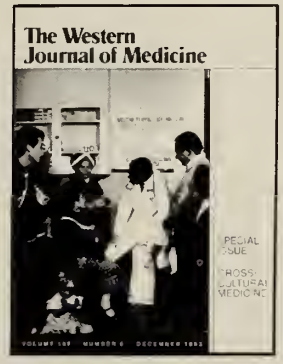

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—Malcolm S. M. Watts, MD

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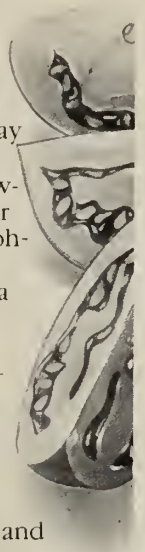

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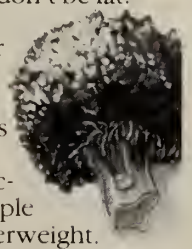
Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.



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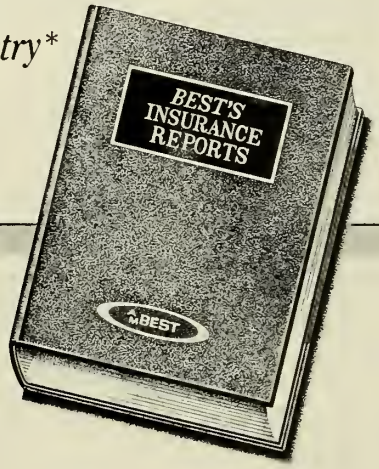

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 4-9, 1988, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1988, date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1988, date and place to be announced.

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New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1988, Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1988, date and place to be announced.

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Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and *uncomplicated)* caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and *rectal)* caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

SURGICAL PROPHYLAXIS. Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e g , vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e g., during coronary artery bypass surgery)

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients This appears to be reversible on discontinuation of therapy In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum

ROCEPHIN® (ceftriaxone sodium/Roche)

duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin Exercise caution before administration to hyperbilirubinemic neonates, especially prematures

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions which were considered to be related to Rocephin therapy or of uncertain etiology were observed

LOCAL REACTIONS— pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%) thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia neutropenia lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting and dysgeusia

HEPATIC— elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM— headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia a decrease in the prothrombin time jaundice, gallbladder sludge glycosuria, hematuria anaphylaxis, bronchospasm serum sickness, abdominal pain, colitis, flatulence dyspepsia palpitations and epistaxis

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg 500 mg 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION)

Also supplied as a sterile crystalline powder as follows

ADD-Vantage Vials** containing 1 gm or 2 gm equivalent of ceftriaxone

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 9 gm dextrose hydrous USP added

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 2 gm dextrose hydrous, USP added

NOTE Rocephin in the frozen state should not be stored above -20°C

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†Manufactured for Roche Laboratories, Division of Hoffmann-La Roche Inc , by Travenol Laboratories, Inc , Deerfield, Illinois 60015

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* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

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Please see adjacent page for summary of product information.